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VOLUME 79 December, 1944 NUMBER 6

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EXPERIMENTAL STRUCTURAL ALTERATIONS IN THE BRAIN DURING AND AFTER CONCUSSION

W. F. WINDLE, Ph.D., R. A. GROAT, Ph.D., and C. A. FOX, Ph.D., Chicago, Illinois

THE literature of brain concussion is voluminous, but this is a deceptive indication of the number of constructive investigations undertaken. It is surprising that relatively so much of a purely metaphysical nature has been published on this vital topic and astonishing that a good deal of it is still accepted and quoted uncritically.

Concussion is a transient state which sets in immediately upon application of an adequate force to the brain. Its chief functional manifestations are unconsciousness and paralysis of certain neural components. Its histopathologic counterpart is a subtle intraneuronal disorganization which will be described here for the first time. The period following subsidence of the functional alterations of concussion should be called postconcussion. In it occur morphologic, perhaps also functional, sequelae of concussion.

In many head injuries, concussion is combined with traumatic interstitial hemorrhage, contusion, or laceration of the brain. The latter three types of injuries should not be given the unmodified designation, concussion, nor should the several post-traumatic conditions be referred to loosely as concussion. Indiscriminate use of the term concussion and its equivalents has produced much confusion in the realm of traumatic brain injuries and their sequelae. Whatever the true distribution of cause and effect in this state of affairs, the fact is apparent also that certain fundamental questions have received little serious attention in the experimental laboratory.

The purpose of the present investigation was to try to demonstrate a structural basis for the physiologic manifestations of pure concussion (8, 10, 24) and to correlate with these findings the histopathologic picture in postconcussion.

MATERIALS AND METHODS

The guinea pig was chosen for the experimental animal because some knowledge of its brain had been gained previously in a study of asphyxial changes (25), and because the brain is not too large to be serially sectioned and stained. Young adults weighing 300 to 400 grams were selected. The experimental series consisted of 36 specimens receiving concussions. For control, 14 normal animals were paired according to size and sex with 14 of the experimental animals and received the same treatment except for concussion. All served for functional comparison, and

From the Institute of Neurology, Northwestern University Medical School.

The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Northwestern University.

For preliminary reports see Windle, Groat, and Fox (26).

brains of 7 were stained for histologic comparison. It was possible to use series of sections of these 7 specimens as normal controls in staining brains of experimental animals which had not been paired directly with controls of their own. In addition, 8 guinea pigs of similar size with hemisection of the first cervical segment of the spinal cord and numerous younger animals which had been asphyxiated and resuscitated at birth served to compare effects of axon section and primary asphyxial changes with those of concussion.

In 33 experiments the guinea pig was first anesthetized lightly with chloralosane, then suspended by two cords, one attached to each forelimb. Connecting the cords was a thread which was hooked under the upper incisor teeth. The thread was so placed that the animal's head was held with its rostrocaudal axis vertical. The vault of the calvarium, with scalp intact, was then struck by the blunt metal end of a pendulum, used previously to produce concussion in cats (10). A stop interposed in the path of the rigid shaft of the pendulum halted it abruptly after the striking end had traveled a few centimeters beyond the point of first contact with the head. The animal was allowed to swing forward against a heavily padded stop. Immediately following the blow the guinea pig was laid on a table and the state of cornea, startle and pinna reflexes, respiration and somatic activity observed and recorded. Abolition of the cornea reflex served as an arbitrary functional criterion of concussion. In 3 other experiments, unanesthetized animals were held in the hand and struck once on the head with a board 2 inches wide, ¾ inch thick.

Nine animals in the anesthetized series were struck two to four blows, each separated from the preceding by 15 minutes or longer. All the other animals were struck only one blow. Comparison of the physiologic results of concussion with and without anesthesia will be made elsewhere.

Fixation was accomplished by vascular perfusion with 1 per cent sodium chloride solution to wash out blood followed by 10 per cent formalin at 92 millimeters of mercury pressure. In 5 instances, the heart was cannulated for perfusion before concussion and the blows struck at intervals ranging from 8 to 30 seconds (perhaps less) before the formalin reached the brain. These, and two intact specimens dealt immediately fatal blows and then perfused, provided material for observing the immediate changes in concussion. The remaining animals were given anesthetic doses of nembutal 4 hours to 32 days after striking the head and were fixed by perfusion.

Brains and spinal cords were removed with care, placed in formalin for 24 to 36 hours and embedded in low viscosity nitrocellulose. One week after killing, the brains were sectioned serially at 40 μ. Every 2 millimeters, four 20 μ sections were cut. Every tenth 40 μ section was removed from the series and stained by a method for Nissl substance of nerve cells. Later, 20 μ series from 8 of the brains were prepared by the same technique. The Weil method (23) for myelin sheaths and the Davenport procedure (7) for axis cylinders of nerve fibers were used with 20 μ sections of the brains from animals receiving strong pendulum blows only and for one normal control.

Sections were cut at 20 μ from each of 4 levels of the spinal cord. These were C1-2, C5-6, midthoracic, and middle of the lumbar enlargement. Nerve-fiber stains were not used for spinal cord sections below C1.

The method for Nissl substance of nerve cells was designed to insure uniformity of staining and thus allow critical comparison of one series with another (27). It employs 0.025 per cent to 0.05 per cent solutions of thionin made up in buffers of *p*H 3.5 to 5.0.[1] In the present series of preparations, a range of *p*H 4.05 to 4.9 was used. By this method staining is carried progressively to completion and decolorizing with acid solutions is unnecessary. To make doubly certain of comparability, sections from experimental and control animals were stained together in the same dish.

RESULTS

Twenty-nine guinea pigs were struck blows ranging from too light to produce symptoms of concussion to very strong and were permitted to live 4 hours to 32 days. All except-

[1]It is important to use the Biological Stain Commission certified dye and to use an acetate, rather than phosphate, type of buffer.

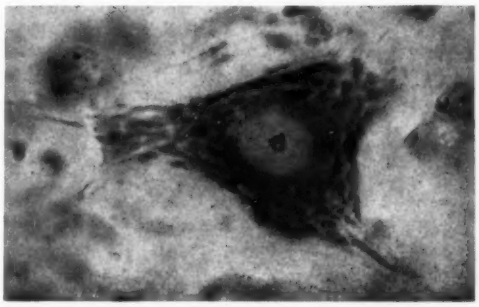

Fig. 1.

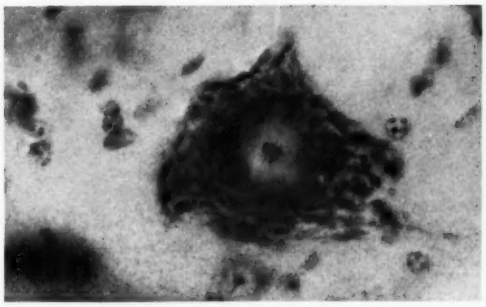

Fig. 2.

Figs. 1 and 2. Large tegmental cells from the brain stem of a normal control guinea pig. Magnification 278×.

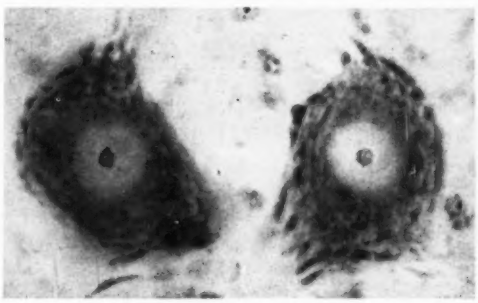

Fig. 3.

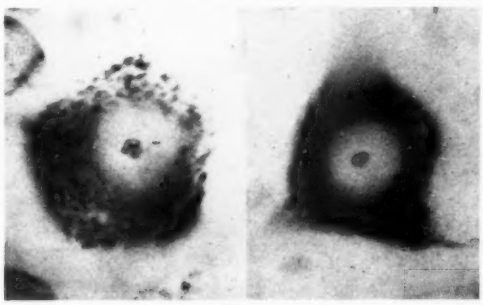

Fig. 4.

Figs. 3 and 4. Four large tegmental cells from the brain stem of a guinea pig which received a concussive blow and was killed by perfusion with formalin a few seconds later. Disorganization of the Nissl-body pattern can be seen. The cell pictured on the extreme right shows that some agglutination of the fragmented Nissl bodies and hyperchromatic staining had occurred. Magnification 278×.

ing 2 which received only single, light, subconcussive blows showed definite cytopathologic changes in the brain which appeared to be the direct result of the blows. The cell changes after the first day were similar in all specimens, varying only in extent and intensity with the severity of the blow and the time after striking it. Although they were observed in neurons of all sizes, large cells, such as those of the red and lateral vestibular nuclei, demonstrated the effects of concussion most clearly.

Within 24 hours after striking a strong blow upon the head, disintegration of Nissl bodies, i.e., chromatolysis, could be clearly observed. The 4-hour specimen resembled those killed by blows (see page 566), but at 14 and 15 hours, disorganization of the Nissl-body pattern and even beginning lysis could be determined. Certain neurons of all the 14 hour to 1 day animals exhibited shrinkage and hyperchromatic staining. These were located among cells which showed beginning chromatolysis, in fact, they themselves showed disorganization of the pattern of Nissl bodies. By 2 days many cells showed marked changes, reaching maximum intensity by the sixth or eighth day. Progressive chromatolysis, like that illustrated in Figures 6 to 15, culminated in destruction of some neurons; not all were affected so severely. Within a group of functionally similar nerve cells 6 to 8 days after concussion, some were so badly damaged that they could scarcely be expected to survive (Figs. 13 and 15), while others were only moderately affected and many were entirely normal in appearance even after the most severe blows. About half the cells of a nucleus was the greatest proportion affected in any experiment (Figs. 16 and 17).

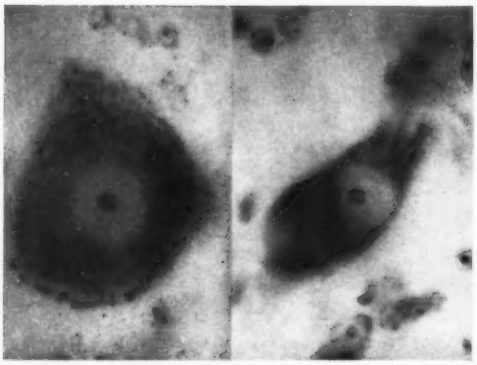

Fig. 5.

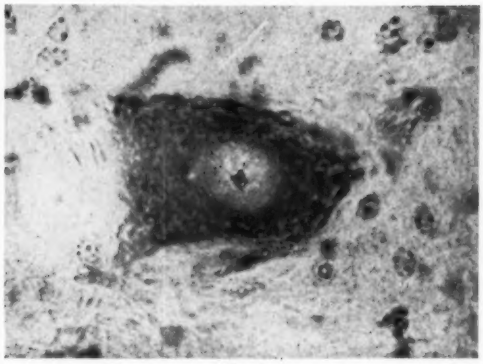

Fig. 6.

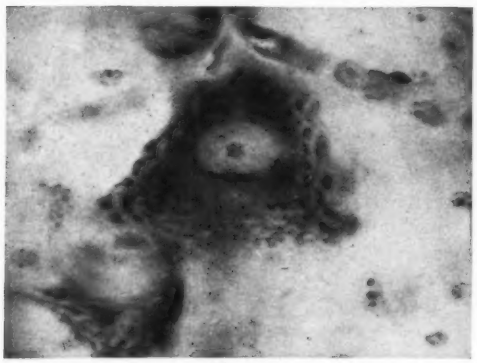

Fig. 7.

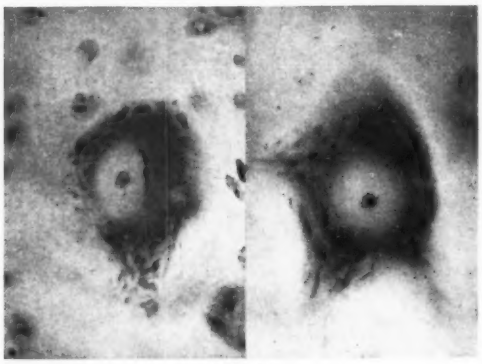

Fig. 8.

Figs. 5 to 8. Large tegmental cells from the brain stem of guinea pigs receiving concussive blows 24 hours previously. The beginning of chromatolysis is illustrated in these six cells. Magnification 278×.

Critical comparison of the chromatolytic picture after concussion with that after transection of nerve fibers, i.e., the axon reaction, and after asphyxia revealed significant differences. After sectioning the axon near the cell body, chromatolysis could not be observed until the end of the second day; after concussion, it could be detected at 14 hours; and after asphyxia, the cytoplasmic changes preceding a true chromatolysis were seen as early as 3 hours. After axon section, chromatolysis began as a breaking up of Nissl bodies around the nucleus and in the cytoplasm adjacent to the axon hillock. After asphyxia, it was frequently initiated as a peripheral clear zone with subsequent vacuolization at the periphery and over-all lysis as early as 30 hours. Concussion, on the other hand, led to a more uniform alteration of the chromatic substance in the early stages. Comparison of Figures 18 to 21 reveals the differences between axon reaction, asphyxial and concussion changes commonly found. Eccentricity of the nucleus, a frequently encountered feature of chromatolysis in the axon reaction, was only occasionally evident after concussion and asphyxia. These and other observations suggested that, whatever the reason for chromatolysis after concussion, it is not asphyxia or primary damage of nerve roots and tracts leading to the axon reaction.

Other evidence was brought to bear upon this question. Sections from brains of severely concussed animals killed after 6 to 32 days were stained by methods for myelin sheaths and axis cylinders of nerve fibers. Nowhere

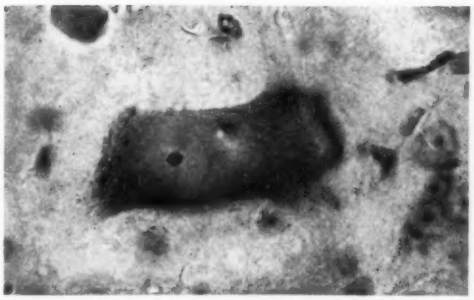

Fig. 9.

Fig. 10.

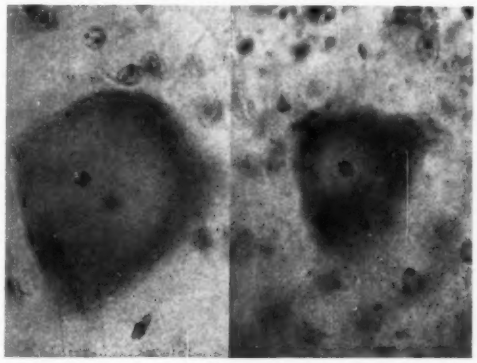

Fig. 11.

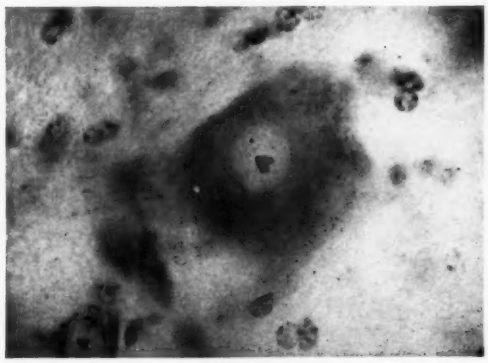

Fig. 12.

Figs. 9 to 12. Large tegmental cells from the brain stem of guinea pigs which received concussive blows 4 days previously. Marked chromatolysis is evident in five of the cells which are illustrated. The one on the right in Figure 10, which is out of focus, was not affected. Magnification 278×.

was massive degeneration of fiber tracts seen. In the animals which were struck the most severe blows, a variable amount of swelling was observed in sheaths of nerve fibers in the lower medulla oblongata and upper cervical spinal cord. Lower reaches of the cord were less affected. Damage in the cord appeared to be confined to deeper parts of the ventral and lateral funiculi. The peripheral zone and the dorsal funiculi were spared. The axis cylinders of fibers appeared to be little, if any, affected. Swelling of myelin sheaths was found as early as 2 days after concussion.

There appeared to be no close relation between the fiber damage and the cell change for there was no significant primary injury of nerve bundles or tracts in many brains which exhibited marked chromatolysis. Furthermore, if the cytopathologic changes were due to tension upon the cranial nerve roots, they should have been most marked in the motor nuclei of the brain and the sensory cranial ganglia because these are the sites of the cell bodies of the root fibers. The semilunar ganglia were left attached to most brains. Their cells were unaffected by concussion. Chromatolysis was observed in primary motor neurons of cranial nerve nuclei in only one instance of very severe concussion, and there it involved only an occasional cell.

A direct approach appears to have given the clearest proof that certain nerve cells are the elements affected immediately in simple concussion. In 5 experiments, it was certain that formalin reached the brain through its blood vessels 8 to 30 seconds (perhaps sooner) after the head had been struck. Comparison with nonconcussed controls stained at the same *p*H demonstrated significant alterations in arrangement, shape and size of

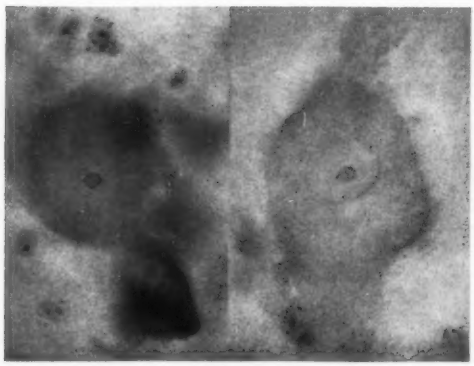

Fig. 13.

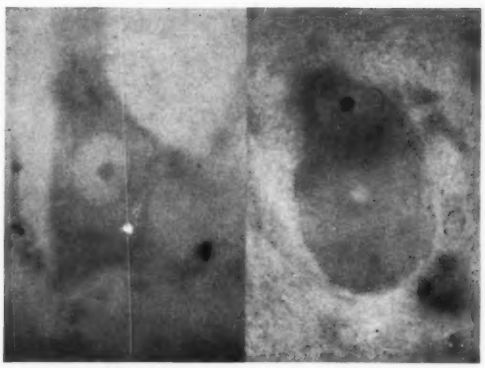

Fig. 14.

Fig. 15.

Figs. 13 to 15. Large tegmental cells from the brain stem of guinea pigs receiving concussive blows 6 days (Figs. 13 and 14) and 8 days (Fig. 15) previously. Extreme degrees of chromatolysis are illustrated. A portion of a relatively normal cell is seen on the left of Figure 13, somewhat out of focus. Magnification 278×.

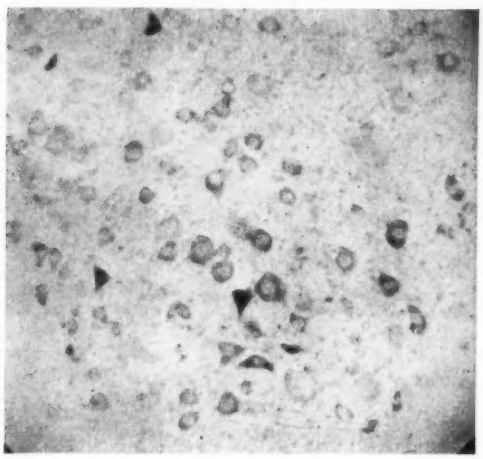

Fig. 16.

Fig. 16. A low power view of the red nucleus 4 days after concussion of a guinea pig. Note the large proportion of pale-staining, chromatilized cells. Magnification 90×.

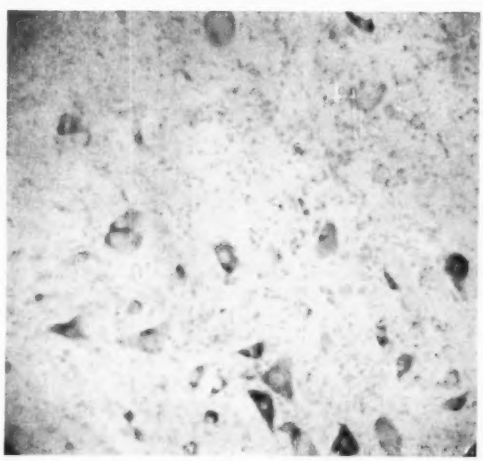

Fig. 17.

Fig. 17. Dieter's nucleus from the same guinea pig as illustrated in Figure 16, 4 days after concussion. Magnification 90×.

Nissl bodies of many neurons of the same nuclei which were observed in chromatolysis a day or more after concussion. It seemed that the Nissl bodies of some cells were fragmented and disarranged by the blow; in other cells, their particles gave the appearance of agglutination. Many neurons remained unaffected. The changes in question are illustrated in Figures 3 to 5. Comparison with controls (Figs. 1 and 2) shows disturbances of Nissl-body patterns. In 2 animals killed by strong blows and perfused as quickly as possible, similar changes in Nissl-body arrangement were encountered. Nucleolar changes were seen in many cells of animals living a day or less after concussion. Many of the Nissl-body changes seen 14 hours to 1 day after the blow resembled those immediately afterward.

The amount of damage was proportional to the strength and number of blows. The greatest amount of chromatolysis followed multiple and single strong concussive blows.

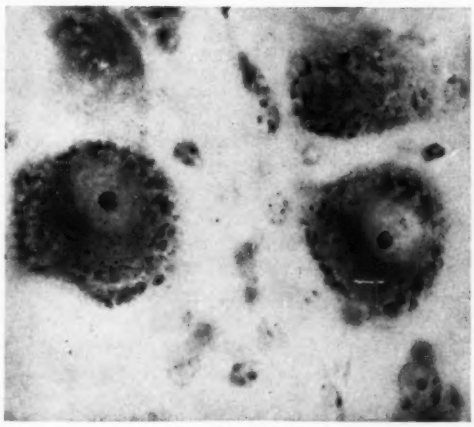

Fig. 18.

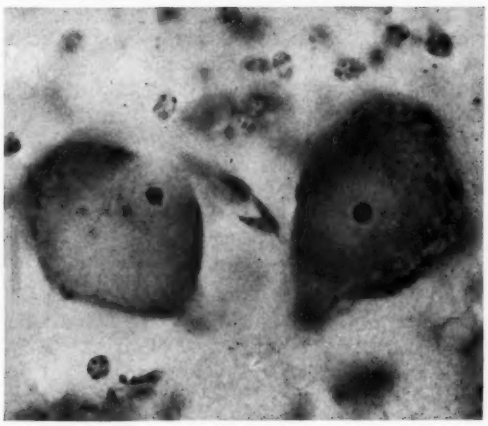

Fig. 19.

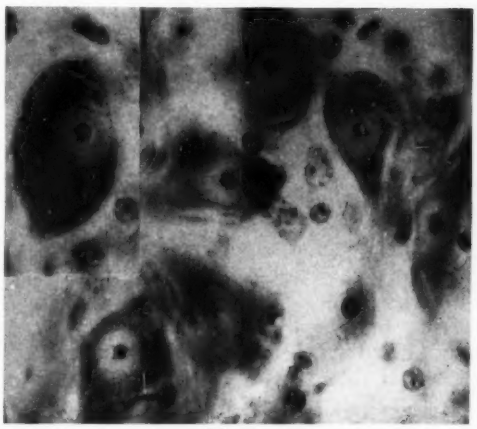

Fig. 20.

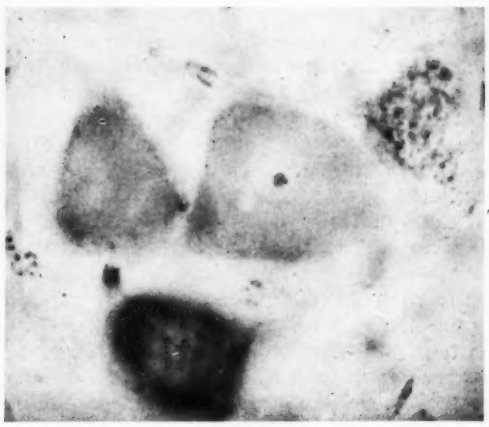

Fig. 21.

Figs. 18 to 21. Four photomicrographs to illustrate the differences between effects of sectioning the axon, asphyxiation and concussion. All are cells of the red nucleus. Figure 18 is from a normal control animal. Figure 19 is from a guinea pig in which the rubrospinal tract was severed 4 days previously. Figure 20 is from an animal asphyxiated and resuscitated 4 days previously. Figure 21 is from an animal receiving a concussive blow 4 days previously. Figures 18, 19 and 21 are from young adult animals; Figure 20, a newborn. Magnification 278×.

A single subconcussive blow was ineffective in 2 of 3 animals but 2 subconcussive blows in 1 animal produced as much chromatolysis as a single light concussive blow in 3 others.

In no instance was destruction of neurons observed in the cerebrum, basal ganglia or cerebellar cortex. Some of the severely affected animals showed alteration of the Nissl-body pattern of large pyramidal cells. These neurons exhibited thickening of nuclear membrane and clumping of Nissl bodies. The cells stained darkly and only rarely could a hypochromatic cell, suggestive of chromatolysis, be found. The changes were not very marked; in fact, they were not definitely identified until after we had examined sections from the cerebrum of monkeys which had received concussive blows. The cortical cells of monkeys are much larger than those of the guinea pig and consequently show the changes better.

In the guinea pig, the main damage appeared to be confined to the brain stem and

spinal cord. Furthermore, certain nuclei only were affected. All concussive blows induced changes in the lateral vestibular nuclei and the scattered large neurons of the tegmentum of the midbrain and pons and reticular formation of the medulla oblongata on either side of the median raphé. With increasing severity of concussion, the red nuclei, nuclei of the trigeminal spinal tract, medial vestibular and cochlear nuclei became involved. In 1 instance 2 days after a very severe, petechial-hemorrhage inducing blow, an occasional primary motor cell in the oculomotor and facial nuclei was found to be chromatolyzed. Otherwise no primary motor neurons of the brain stem were damaged. It was interesting that proximity to the ventricles was not a factor governing occurrence of damage.

Changes were observed in the spinal cord. Nearly all specimens which exhibited chromatolyzed cells in the reticular formation of the medulla oblongata had a few cells affected in the posterior horn of the upper cervical segments. Those with more severe damage in the brain stem also showed marked spinal cord changes. In several animals, neurons of the anterior horns were chromatolyzed in the cervical region, although the posterior horns were more involved. A rather good correlation was drawn between severity of cytopathology and degree of motor disability in the first 2 days after concussion. The animals showing marked spinal motor weakness also exhibited the most structural damage in the spinal cord. Those which showed no motor symptoms on the second day had no chromatolysis in the anterior horn cells.

Controls exhibited no chromatolysis. The occasional degenerating neuron found in normal adult brains was not encountered in the nonconcussed control guinea pigs of the present series. These were young sexually mature animals which had not attained maximum growth. The animals which had received no anesthesia showed as much damage as those anesthetized.

Hemorrhage was an unimportant component of the pathologic picture after experimental concussion. Hemorrhages, mostly very small and insignificant points of bleeding into the meninges or outside the dura mater, were encountered in a number of the guinea pigs after strong blows upon the head. Extensive meningeal bleeding occurred only in 2 which were killed by blows. Intramedullary hemorrhages were found in 4 specimens receiving very strong nonfatal blows. In 1, a few petechiae were located in the anterior thalamus, hypothalamus, rostrum of the corpus callosum and upper cervical spinal cord. In the others, small interstitial hemorrhages were found in the cervical and thoracic spinal cord. The cytopathologic changes under discussion were never associated with hemorrhages.

No evidence of brain edema due to striking blows upon the head was observed in the histologic preparations. At no time after concussion did a marked glia reaction appear. After 1 week, a limited proliferation of astrocytes was observed in the animal receiving the strongest blows, but the microglia appeared to be no more numerous than in controls. In this respect as well as in absence of hemorrhage and lack of evidence of edema, the histopathology after pure concussion was unlike that after asphyxiation (25).

DISCUSSION

Previous articles dealing with histologic changes in the brain after conditions designated as concussion have revealed variously no alterations, cell changes, fiber changes, and small hemorrhages. Every such study which has been found in the literature is open to criticism. On the face of the available reports it is impossible to arrive at any other conclusion than the vague notion that concussion involves widespread and generalized primary and secondary cell and fiber degeneration and hemorrhages; against this, is the view of other writers that concussion is purely functional with no anatomical substratum.

The haze lifts considerably with realization that in only one instance (8) have investigators discussing histologic changes in concussion defined the latter term. In all cases in which hemorrhages are described as part of the concussion picture, it is clear that, while such hemorrhages are an indication of the severity or peculiarity of the injury, they do not necessarily bear further relationship to the condition of concussion that

may have occurred. The extensive "Duret hemorrhages" which Berner (2, 3) has confused with concussion attest to the severity of the injury. Berner's material consisted of postmortem cases in which patients died as a result of head injury. But the injury was certainly not pure concussion. It was concussion plus traumatic interstitial hemorrhage. The former (in its true sense) as well as the latter may have been instrumental in causing death. Much the same comment applies to Neugebauer's work. Many of his patients were perhaps more intensely injured than Berner's, and consequently the hemorrhages were somewhat more generalized in the brain stem. The excellent investigations of Schaller, Tamaki and Newman (20, 21) of the genesis and significance of multiple petechial hemorrhages are likewise beclouded by the unfortunate misuse of the word, concussion, when the injuries clearly were complicated. Autopsy studies serving as the basis for elaborate theories of circulatory disorder in the so called postconcussional state, e. g., Friedmann and Rosenhagen, are similarly vitiated by complications and doubtful concussion.

Reports of cell and fiber alterations are gapingly open to criticism (4, 6, 12, 15, 19, 22). The injuries were not concussion or were not described and hence cannot be evaluated as concussion, the methods used were inadequate, and controls were lacking.

Nimier wrote of a single case of suicide by rifle bullet through the head as concussion. Whether a concussion existed or not, he was unable to find microscopic lesions upon histologic examination of all parts of the brain outside the path of the bullet. Recently Denny-Brown and Russell were unable to find evident microscopic lesions in the material from their acute animal experiments. These and other similar reports do not mean that there were no changes, but simply that the nature of the examinations was such that changes were not revealed. The work of Koch and Filehne has been cited as evidence that concussion can occur without any anatomic changes, but it is not clear that these workers used a microscope. Nor is it clear that the condition which they and others produced by striking many light, rapidly repeated blows should be considered analagous to the concussion produced by one severe blow, whether this is the initial one or not.

The results of Jakob and of Brunner are the only ones which merit detailed discussion. Neither investigator defined concussion but Jakob did give descriptions of the gross functional effect of blows. In most cases these are sufficient to serve as a basis for characterizing the blows as concussive or nonconcussive. Jakob studied the central nervous system of 14 rabbits and 3 monkeys removed at various times after the animals received one or more blows on the fixed head. In the rabbit series, he found no microscopic changes in 3 animals which died within 2 minutes after concussive blows were struck. Neither did he find changes in 1 animal sacrificed 24 hours after a nonconcussive blow. The remaining 10 animals received from 3 to 84 blows, the larger number being delivered over several days, and were sacrificed 6 to 81 days after the beginning of the experiment. The most constant alteration was degeneration of nerve fibers. Glia changes were quite regularly found. They were either regressive changes and proliferation or aggregation of débris-gorged glia in vessel sheaths. Nerve-cell changes were found in 6 animals from 6 to 59 days after the first injury. In 3 of these instances, concussion had been sustained; in 2 others, it was doubtful; and in 1 which received 29 blows, it was absent. Of the remaining 4 rabbits, 1 received 10 blows, no concussion, was killed after 13 days, and showed fiber degeneration; 1 received 3 blows, no concussion, was killed after 31 days, and was studied only for Marchi degeneration which was present; 1 received 5 blows, concussion, was killed after 150 days, and showed fiber degeneration; the last received 84 blows, no concussion, was killed after 81 days, and showed very many scattered small hemorrhages with softening of different ages and glia proliferation with ameboid glia present.

The fiber degeneration which Jakob found was heaviest in the medulla oblongata and cervical spinal cord, particularly in the longer ascending and descending tracts. Above and below these regions it tended to grade off. Degeneration was visualized by the Marchi

method. The histologic reaction accompanying degeneration, as shown by other methods, was described at length. The nerve-cell changes were diffuse. In the two 6-day animals, for instance, profuse chromatolysis was reported in all of the basal nuclei, thalamus, red nucleus, pons, medulla oblongata and anterior horn of cervical spinal cord. It was especially severe in the cranial nerve nuclei of the medulla oblongata.

It is evident that Jakob's findings in regard to cell changes are at variance with those of the present work. Some of the discrepancy may be a consequence of the rather impractical method of inflicting injury which Jakob employed. Most, however, appears to result because Jakob's animals were not fixed by perfusion and because he did not use controls.

Jakob used 3 monkeys for concussion, a fourth as control. The control died and the central nervous system was removed while the animal was still warm. All the monkeys received multiple blows, doubtful concussion, and presented the complications of infection and malnutrition. They were killed 8, 16 and 44 days after the injury. Because of the complications which were aggravated after the injury, Jakob felt that he could report only on the Marchi degeneration, which was present as in the rabbits.

Brunner's primary interest was concussion of the inner ear. He used 7 guinea pigs, striking repeated blows on the fixed head. The brain stem and cerebellum of 4 were studied histologically by a method for Nissl bodies only. One guinea pig was used as a control for these histologic studies. One animal was killed 2 days after sustaining 10 blows. Here there were glia changes, neuronophagia, and small hemorrhages in the tuberculum acusticum and degeneration of cells of the cochlear and vestibular nuclei. A second animal received 7 blows in 2 days and was sacrificed 4 days after the first. It was perfused. There were glia changes and light chromatolysis in the cochlear and vestibular nuclei, especially in the medial vestibular and ventral cochlear nuclei. The small cells were the only ones said to be affected; the large and medium sized neurons were normal. The third animal suffered 20 blows. Perfusion was performed, but the author stated that fixation was so poor that the distinction between pathology and artifact was difficult. Chromatolysis, glia changes and neuronophagia were seen with certainty only in the region of the large cells of Deiter's nucleus. The last animal was struck 15 blows and killed 74 days later. Small hemorrhages of old standing, thought to be the result of diapedesis, were found in the brain stem. Surrounding cells were unharmed. Widespread glia proliferation and chromatolysis of nerve cells were observed in the brain stem. Here again the findings differed from those of the present work and undoubtedly for the same reasons which were applied in the résumé of Jakob's work. True, there was a control animal, but the controlling activity apparently went no further than just that. Two of the experimental animals were perfused but the perfusion technique must have been inadequate since, by the author's admission, one of these was very poorly fixed.

A further criticism of Jakob's and Brunner's reports is their failure to relate anatomic changes of the postconcussion period to anatomic and physiologic changes of concussion. This correlation can be drawn in our work. Results of previously published physiologic studies are compatible with the currently reported concussional and postconcussional histologic findings. Groat, Magoun, Dey and Windle (10) observed that, in brain concussion of the cat, excitability of such supranuclear motor regions as the cerebral cortex, hypothalamus and brain-stem tegmentum was decreased while functional alteration of cells of cranial motor nuclei was less constant and less severe. Nerve fibers in the brain rarely exhibited decreased conductivity. By comparison of certain reflex activity with the excitability of the corresponding motor cell group in the brain stem, it was concluded that reflex inactivation in concussion was due primarily to interneuronal dysfunction.

Our inability to find marked damage of nerve fibers or their myelin sheaths after concussion can be correlated with lack of functional changes. Our physiologic studies demonstrating only slight and transient impairment of excitability of primary motor neurons are in full accord with the present

finding of little or no structural change in cells of cranial motor nuclei. The structural changes were indeed confined to interneurons which may be the reason for marked impairment of function shown by our physiologic studies.

Not all interneurons of the brain appear to be damaged by concussion; at least, we were unable to observe frank changes in all. This was notably true of the higher centers and the cerebral cortex. An effort was made to report damage only when, by careful comparison with controls, it seemed unequivocal. In many instances we could find neurons which we thought exhibited structural alterations but which, in normal material, possessed irregular or indistinct Nissl-body arrangements. That we may have been overly cautious has been demonstrated in the cerebral cortex. The larger pyramidal neurons in the monkey clearly showed changes after concussion (11) although examination of the same neurons in the guinea pig left a feeling of uncertainty. Little has been said of the small nerve cells. It is difficult to tell when they are affected because many have scanty Nissl material normally. Possibly careful cell counts in selected regions would reveal fewer small neurons after a week or two.

The present observation of immediate cell changes is, so far as we have been able to determine, new. However, it is not surprising to find disorganization of Nissl bodies, especially the large flakes of large neurons, in concussion; others (1) have demonstrated that Nissl bodies have a structural representation in the unfixed nerve cell and can be caused to stratify by centrifugation. In our experiments, these bodies did not become stratified but they apparently were fragmented and otherwise affected by the force applied. What is rather surprising is that not all nerve cells in a group of functionally similar neurons were equally affected by the blow. This is correlated with the fact that, later, chromatolysis was found in only certain cells of a group.

The nature of the disability which lies at the bottom of the altered function in concussion can only be guessed, for the relation of the subtle immediate histologic changes to the functional phenomena is unknown. These histologic changes do serve as visible indicators of the ravages of a concussional force and they mark the points at which postconcussional loss of cells will occur. The number of cells lost in postconcussion is probably only a fraction of the number functionally altered in concussion. It is reasonable to suppose, tentatively, that all the neurons are exposed to the concussive force to some degree, that certain groups of cells are more susceptible than other cell groups and fibers and that, depending upon their condition at the time of application of the force, some of the susceptible cells are irreversibly injured. This number varies directly with the intensity and number of concussions but probably is automatically confined below a definite upper limit by the intervention of death if the immediate cell damage attains a certain lethal level. The part which the neuron loss might play in the post-traumatic condition following pure or complicated concussion is debatable.

Though the word, concussion, has served only as a source of confusion in the past there is no reason why it should not be redeemed and employed to denote a discrete and specific, though transient, pathologic condition. At least such would appear desirable pending additional information and experience. At some arbitrary state, concussion passes into postconcussion. Only in uncomplicated concussion can the functional course of this transition be seen. It is the time when the subject begins to react to incoming sensory impulses at all levels. It is only later in postconcussion that frank degeneration of numerous nerve cells can be seen. The significance of the cytopathologic alterations of concussion and postconcussion has yet to be determined.

SUMMARY

Brain concussions were produced in guinea pigs by striking blows of graded intensity with a pendulum-like apparatus. Most animals were lightly anesthetized with chloralosane and were permitted to live for varying periods up to 32 days after concussion. The animals were then anesthetized with nembutal and killed by perfusing the heart with 10 per cent formalin. Brains and spinal cords were sectioned serially and prepared for histologic study. Staining was controlled.

In a few experiments, the brain was fixed by perfusion with formalin within a few seconds of the time a concussive blow was struck upon the head. Significant alterations in arrangement, shape and size of Nissl bodies of neurons were observed in these specimens. The Nissl bodies of some of the cells appeared to be fragmented and disarranged by the blow. In other cells their particles gave the appearance of agglutination. Many neurons remained unaffected. Similar changes were observed in animals killed by strong blows and perfused immediately, as well as in others which lived for a day or less after the blow.

In less than 24 hours after concussion, chromatolysis of certain neurons began. By 2 days many cells showed marked changes, reaching maximum intensity by the 6th or 8th day. Progressive chromatolysis culminated in destruction of some neurons but not all were affected so severely. Chromatolysis after concussion differed significantly from that observed after sectioning nerve nerve fibers and that seen in asphyxia.

In most of the experiments, nerve fibers and myelin sheaths appeared to have received little, if any, damage. In those specimens which were struck the most severe blows a variable amount of swelling was observed in myelin sheaths, especially in the lower medulla oblongata and upper cervical spinal cord. There appeared to be no correlation between fiber damage and the cellular changes.

All neurons were not equally affected in concussion. Primary afferent and primary efferent neurons of the cranial ganglia and cranial nerve nuclei were practically unaffected. All concussive blows induced changes in the lateral vestibular nuclei and the scattered large neurons of the tegmentum of the midbrain, pons and reticular formation of the medulla oblongata. With increasing severity of concussion, the red nuclei, nuclei of the trigeminal spinal tract, medial vestibular and cochlear nuclei became involved. Large pyramidal cells of the cerebrum underwent alterations but did not show chromatolysis. The basal ganglia and cerebellar cortex appeared to be unaffected. The amount of damage was proportional to the strength and number of blows struck.

Hemorrhage was an unimportant component of the pathologic picture in and after concussion. Rarely was intramedullary hemorrhage noted and meningeal bleeding occurred only in 3 animals killed by blows. The cytopathology was not the result of hemorrhage.

The cell changes observed in concussion of guinea pigs are in every way compatible with the functional observations in and after concussion of the cat. Studies in the monkey now in progress show similar results. All experiments were thoroughly controlled.

REFERENCES

1. Beams, H. W., and King, R. L. J. Comp. Neur., 1935, 61: 175–189.
2. Berner, Ole. Virchow's Arch., 1930, 277: 386–419.
3. Idem. Am. J. Surg., 1935, 29 (n.s.): 273–281.
4. Bikeles, G. Zbl. Nervenh. Psychiat., 1894, 17 (n.f. 5): 408–410.
5. Brunner, Hans. Mschr. Ohrenh., Wien, 1925, 59: 697–709, 763–833, 922–937.
6. Buedinger, Konrad. Deut. Zschr. Chir., 1895, 41: 433–444.
7. Davenport, H. A. Anat. Rec., 1929, 44: 79–83.
8. Denny-Brown, D., and Russell, W. R. Brain, 1941 64: 93–164.
9. Friedmann, M. Arch. Psychiat., Berl., 1892, 23: 230–267.
10. Groat, R. A., Magoun, H. W., Dey, F. L., and Windle, W. F. Am. J. Physiol., 1944, 141: 117–127.
11. Groat, R. A., Windle, W. F., and Magoun, H. W. J. Neurosurg. In press, 1945.
12. Gutiérrez-Mahoney, W. de. War Med., Par., 1941, 1: 816–823.
13. Jakob, Alfons. Histologische und histopathologische Arbeiten ueber die Grosshirnrinde. Franz Nissl und Alois Alzheimer. Vol. 5, pp. 182–341. Jena: Fischer, 1913.
14. Koch, W., and Filehne, W. Langenbeck's Arch. klin. Chir., 1874, 17: 190–231.
15. Macpherson, John. Lancet, Lond., 1892, 1: 1127–1129.
16. Neugebauer, Walter. Frankf. Zschr. Path., 1937–1938, 51: 210–236.
17. Nimier, M. J. Ass. Military Surgeons U. S., 1903, 12: 24–26.
18. Rosenhagen, Hans. Deut. Zschr. Nervenh., 1930, 114: 29–73.
19. Scagliosi, G. Virchow's Arch., 1898, 152: 487–525.
20. Schaller, Walter, F., Tamaki, K., and Newman, Henry. Arch. Neur. Psychiat., 1937, 37: 1048–1076.
21. Ibid. 1941, 45: 1–23.
22. Virchow, Rud. Virchow's Arch., 1870, 50: 304.
23. Weil, Arthur. Arch. Neur. Psychiat., 1928, 20: 392–393.
24. Williams, Denis, and Denny-Brown, D. Brain, 1941, 64: 223–238.
25. Windle, W. F., Becker, R. F., and Weil, Arthur. J. Neuropath. Exp. Neur., 1944, 3: 224-238.
26. Windle, W. F., Groat, R. A., and Fox, C. A. Feder. Proc., 1944, 3: 53; Anat. Rec., 1944, 88: 52.
27. Windle, W. F., Rhines, Ruth, and Rankin, James. Stain Technol., 1943, 18: 77–86.

INJURIES OF THE EXTREMITIES IN AMPHIBIOUS WARFARE

JAMES PIERCE COLE, M.D., D.Sc. (Med.), Lieutenant, M.C.-V(S), U.S.N.R., Buffalo, New York, and HARRY BRYAN NEEL, A.B., M.D., M.S. (in Surg.), F.A.C.S., Lieutenant, M.C.-V(S), U.S.N.R., Albert Lea, Minnesota

THE treatment of war wounds is a subject of great interest at the present time, as is evidenced by the large number of articles which are appearing in the medical journals and in the lay press. The conditions under which treatment must be carried out, the wounds encountered, the large number of patients who must be seen in a short period of time, and the psychological reactions of men who have faced an enemy in mortal combat are a few of the factors which influence the treatment of patients wounded in battle.

The purpose of this paper is to present a statistical and descriptive study of patients who received injuries to the extremities while engaged in amphibious warfare. The management of these injuries and of the complications which ensued has enabled us to form impressions and to draw a few definite conclusions.

Of 984 consecutive battle casualties admitted to this hospital ship, 638, or 64.8 per cent, had sustained injuries of the extremities and were under observation for a period varying from a week to 10 days. The time elapsed between the moment of injury and the time of admission was variable and ranged from a few minutes to 4 days. The majority of patients were seen within the first 48 hours, and 28.3 per cent were seen during the first 24 hours (Table I). The observations made on these patients form the basis of this report.

It has been necessary to bring all patients to the ship in small boats and to bring them aboard, except in the case of ambulatory patients, on stretchers. On the quarter-deck each patient was seen by the embarkation officer who appraised the general condition of the patient and the nature and extent of the wounds before despatching the patient to a dressing station or ward, where a medical officer awaited his arrival.

CONDITION OF PATIENTS ON ADMISSION

Inasmuch as many of these patients were admitted directly from the beach, often within a few minutes of the time they were injured, only the most necessary first-aid had been given. Some of the patients had been painted with camouflage paste, many were covered with dirt, often they were wet, and frequently they were plastered with blood and sand. In some instances as many as two extremities had been blown away (Fig. 1) and tourniquets were in place. In other cases, intracranial, thoracic, or abdominal injuries accompanied the injuries of the extremities. Some of the patients with older injuries had previously received excellent treatment at other activities.

In patients with wounds of the extremities 571 (89.5%) were in good general condition on admission. They required no immediate transfusion of blood or administration of plasma. It was not necessary to take them to the operating room for the control of hemorrhage. It was frequently necessary to use morphine sulfate for the control of pain, and this drug was given liberally in doses of ¼ or ½ grain. The treatment of many of these patients could be deferred until the more seriously wounded were cared for. Some required only dressings while others had to be taken to the operating room later for necessary treatment.

Twenty-two patients (3.46%) were in fair condition, requiring plasma and blood transfusions without delay, and 45 (7.05%) patients were in poor or critical condition, immediate and energetic treatment being necessary in order to give them the maximum chance of recovery. Four in the latter group died soon after admission.

CAUSE OF INJURIES

Fragments from shells, bombs, grenades and mortars, and flying débris, such as con-

TABLE I.—TIME ELAPSED BETWEEN INJURY AND ADMISSION

Hours	Number of patients	Per cent of patients
0 to 24	181	28.3
24 to 48	245	38.4
48 to 72	83	13.0
72 to 96	129	20.3
Total	638	100.0

TABLE II.—CAUSE OF INJURY

Missile or agent	Number of patients	Per cent of patients
Fragments	369	57.8
Gunshot	231	36.1
Fragments and gunshot	21	3.29*
Burns, bayonet, sword operational	38	6.1
Total	638	100.0

*Not counted.

crete, were responsible for the wounds in 369 patients, or 57.8 per cent of those wounded. The fragments recovered varied in size from minute particles to pieces weighing as much as a pound, but we are inclined to believe that some of the contusions and fractures were inflicted by even larger pieces of concrete. Rifle and machine gun fire accounted for injuries to 36.1 per cent of patients and 3.29 per cent of the patients were wounded by both fragments and gunfire. Various other instruments of war, such as thermal agents, bayonets and swords, caused the injuries of 6.1 per cent of patients (Table II).

TYPES OF WOUNDS

There is no satisfactory classification for wounds inflicted by missiles which vary so greatly in size, shape, velocity, temperature, and consistency. Some of the patients had received sprays of small fragments and all extremities were occasionally involved. These small fragments penetrated to different depths; some could be picked from the skin, some could be felt under the skin, and others were detected only on roentgenologic examination. In such cases it was unusual for the fragments to disrupt the blood vessels, nerves, or bones, although the joints were occasionally involved. Many of these small wounds could be properly designated as puncture wounds.

Very rarely encountered were the cleanly cut lacerations. The skin edges were usually irregular in outline, ragged, dirty, and sometimes burned. The involvement of the underlying tissues was not necessarily related to the size of the skin wound since the fragment may have turned and presented a smaller or larger diameter after penetration of the skin. As is well known, in bullet wounds the wound of exit was larger than the wound of entrance although in some cases both wounds were

TABLE III.—LOCATION OF WOUNDS IN ORDER OF FREQUENCY

Part wounded	Number of times wounded	Per cent of patients
Upper arm	169	26.48
Lower leg	167	26.17
Thigh	157	24.60
Hand	126	19.74
Shoulder	83	13.00
Forearm	71	11.12
Feet	50	7.83
Knee	38	5.95
Buttocks	38	5.95
Elbow	31	4.85
Total	930	100.00

TABLE IV.—PERIPHERAL NERVE INJURIES

Nerve	Number injuries	Per cent of nerve injuries	Avulsion partial	Avulsion complete	Caused by fragment	Caused by gunshot	Fracture
Brachial plexus	2	3.77	1	1	1	1	1
Radial	16	30.19	10	6	9	7	4
Ulnar	9	16.98	7	2	7	2	5
Median	8	15.10	8		5	3	3
Sciatic	7	13.21	5	2	5	2	2
Lateral femoral cutaneous	2	3.77		2	1	1	1
Common peroneal	5	9.44	2	3	4	1	1
Deep peroneal	2	3.77	2			2	1
Superficial peroneal	2	3.77	1	1	2		1
Total	53	100.00	36	17	34	19	19

TABLE V.—INJURIES TO LARGE BLOOD VESSELS

Vessel	No. cases	Caused by		Fracture present	Disposition
		Fragment	Gunshot		
Femoral	4	2	2	2	2 Amputation midthigh inevitable 2 Amputation
Popliteal	4	3	1	1	2 Amputation low thigh 1 Amputation leg 1 Ligation vein
Subclavian	1	1			Secondary hemorrhage controlled by suture
Total	9	6	3	3	

small and healed promptly. More than half (50.9%) of the wounds were 3 centimeters or more in diameter and many were as much as 400 square centimeters in area. In some patients large flaps of skin and subcutaneous tissue had been avulsed or turned back, and, in a few, lacerations of the skin, fascia, and muscles, especially in the arm, the buttocks, and thigh, had resulted in large gaping wounds which gave the appearance of great loss of tissue. If the wounds involved the deep fascia or deeper structures they were classified as deep wounds, and those in 72.5 per cent of the patients fell into this category. It will be shown later that injuries to bone were sustained by 36.83 per cent of the patients.

LOCATION OF WOUNDS

Statistical tabulation of the wounds showed that the lower and upper extremities were involved approximately equally and that in 12.85 per cent of the patients both the lower and upper extremities sustained wounds. There was very little difference in the number of wounds of the two sides except in the shoulder, arm, and thigh, where wounds of the right side predominated (Table III).

The arm was most frequently injured, 26.48 per cent of patients having been wounded in this area, while the elbow was least frequently injured. The hand was involved in 19.74 per cent of patients, a very high incidence considering the comparatively small surface exposed. Among the patients with injuries of their hands, there were ten whose hands were badly mutilated when they attempted to return enemy grenades, or to recover those fumbled by our own forces.

FRACTURE

Two hundred thirty-five patients who had extremity injuries of the soft tissue had also sustained fractures. One patient had suffered a dislocation of the elbow while 2 patients sustained a fracture dislocation of the hip. The percentage of patients with compound fractures was 92. Very often multiple fractures were present in the same individual. In Table VI the various bones of the extremities are listed with the number of fractures comminuted, compound, or simple in type.

TABLE VI.—DISTRIBUTION OF FRACTURES IN 235 PATIENTS

Location	Number of fractures	Number comminuted	Number compound	Number simple
Scapula	26	18	25	1
Clavicle	7	2	7	
Head and neck of humerus	12	12	12	
Shaft of humerus	47	29	45	2
Radius	19	13	18	1
Ulna	38	24	30	8
Carpals, metacarpals, and phalanges	51	37	51	
Pelvic bones	7	4	5	2
Head and neck of femur	4	2	2	2
Shaft of femur	30	22	29	1
Lower femur	1		1	
Patella	2	2	2	
Tibia	21	13	20	1
Fibula	12	5	10	2
Tarsal bones	7	3	6	1
Metatarsals and phalanges	8	6	7	1
Totals	292	192	270	22

GENERAL TREATMENT

The arrest of hemorrhage and the treatment of shock were, of course, given primary consideration. Tourniquets and pressure dressings usually controlled the hemorrhage; in only a few instances was it necessary to ligate a vessel in order to stop the bleeding, and this was done during the treatment of shock. The combination of circumstances which necessitated operative intervention in wounds of the extremities before adequate treatment of shock presented itself rarely.

When a patient in shock was admitted to the ward, morphine sulfate was given hypodermically for pain, if necessary, unless the patient had been given this drug previously and recently. External heat was applied and the foot of the bed elevated. Plasma was administered in sufficient quantities, as many as 8 units being given to some patients very soon after their admission. Arrangements were made for transfusion of blood.

To all of the battle casualties admitted to this ship (984) nearly 500 units of plasma were administered. We could not determine the exact number used in the treatment of patients with injuries of the extremities alone. Most of this plasma was given during the first 2 days.

Nearly all of the patients in shock had lost blood, and in this type of patient there is no adequate substitute for whole blood transfu-

TABLE VII.—AMPUTATIONS PERFORMED

Site of amputation	Number	Indications			Per cent of amputations
		Gas gangrene	Vascular injury	Irreparable damage, crushing, etc.	
Arm	2	2			5.88
Forearm	1			1	2.94
Fingers	15			15	44.12
Thigh	12	4	4	4	35.30
Leg	4		1	3	11.76
Total	34	6	5	23	100.00

sions. In many instances there was a striking difference in response to plasma and blood. One hundred fifty-seven transfusions were given, all by the indirect method. There was but one serious transfusion reaction.

In summary, the relief of pain, apprehension and fear, the control of hemorrhage, and the restoration of body fluids by the administration of plasma and whole blood were considered prerequisite to the definitive treatment of wounds of the extremities.

TREATMENT OF WOUNDS

When indicated, roentgenologic studies were made before the patient was brought to the operating room. The surgeon was aware of the presence of metallic foreign bodies and fractures, and of nerve, tendon, and vascular involvement.

The skin surrounding the wound was washed thoroughly with soap and sterile water. The wound was then irrigated with copious quantities of sterile normal saline solution. The recesses of the wound were exposed with the sterile gloved hand so that all parts of the wound could be adequately irrigated and cleansed. It was amazing how frequently dirt, grass, pieces of clothing, sand, and burnt tissue were found in the depths of the wounds and in crevices which could be disclosed only by the fingers or an instrument. We feel that the arguments against the irrigation of wounds of the extremities have little basis in fact and we know of no other way in which a wound can be so well cleaned.

TABLE VIII.—AMPUTATIONS PRESENT ON ADMISSION

Site	Number
Arm	2
Forearm	2
Fingers	15
Thigh	4
Leg	3
Toes	4
Total	30

The area was then draped and preparations were made for a surgical procedure under aseptic conditions. The skin edges were trimmed and nonviable muscle and fascia were excised. Bleeding points were carefully clamped and ligated, usually with fine plain catgut. The depths of the wound were then exposed and inspected again in order to be positive that no débris remained. Vaseline gauze was then placed in the wound, following which a large sterile dressing was snugly applied.

Tendon suture was found very infrequently to be indicated in these fresh war wounds. In most of the large wounds of the hand and foot, and in some of those of the forearm and leg, the tendons were badly avulsed and were beyond any possibility of repair. They had to be excised, often with the fingers and toes, but in routine débridement the excision of tendons was as conservative as possible. When the tendons were intact but exposed it was desirable to cover them. In 2 instances this was done in our cases by a sliding skin graft. The only tendon repair in this group of patients was on a patient who had a clean wound of the leg with laceration of the tendons of the peroneus longus and the peroneus brevis. The tendons were approximated with silk and the wound was partially closed. Immobilization was maintained by plaster.

Primary suture of a war wound, although it may appear clean and suitable for such treatment, has been found to be hazardous and is rarely warranted under the prevailing circumstances. We have observed a few wounds that were sutured before reaching us and in a high percentage of cases they became infected and broke down.

What should be the policy in regard to the removal of metallic fragments and bullets? In many cases they are discovered and can be removed easily during the débridement. This is desirable. We feel that it is not wise to

Fig. 1. Photograph of patient who was admitted soon after injury. This photograph illustrates some of the problems encountered in caring for large numbers of fresh casualties.

make an extensive search for a foreign body, opening new planes and traumatizing tissues, and that it is better to leave them until a later date. If a metallic body lodges just beneath the skin and is tender, it becomes advantageous to remove it, and it is necessary to remove those that impinge on large vessels and nerves. In most instances the removal should be undertaken, as indicated, only when the wounds have healed and the possibility of infection is remote.

Even soft tissue wounds of the extremities require immobilization. On this ship such immobilization has best been accomplished by the use of plaster splints and casts. The increase in comfort, the loss of fear and apprehension, and the acceleration in rate of recuperation after immobilization have been repeatedly demonstrated.

CHEMOTHERAPY

Probably no other group of drugs has ever been received with such widespread acclaim as have the sulfonamides. Lowered morbidity and mortality in both battle casualties and accidents of civil life have been attributed to the efficacy of the sulfonamides. In recent months, however, some doubt has arisen as to the value of these drugs in the treatment of war wounds when applied topically or when administered for their general effect or by both methods. Because of many factors it was not possible to determine with accuracy the effect of sulfonamides; consequently more than a comment regarding their use may be misleading. We have observed many wounds into which has been placed sulfonamide and in some of these the powder had become caked; there was much discharge and the tissues appeared indolent. Removal of these lumps and the cleansing of the wound were followed by rapid and marked improvement. We believe very strongly that if sulfonamides are to be used for topical application, the more readily soluble forms should be used and then only with great care so that the drug may be distributed evenly throughout the extent of the wound and not "dumped" in so as to act as a foreign body. The absence of spreading pyogenic infection and septicemia in this group of patients was noteworthy and it is possible that these results were achieved to a great extent by the use of sulfonamides. It has been our impression, however, that occasionally there has been so much reliance placed on the efficacy of sulfonamides that the accepted and

Fig. 2. Roentgenogram of a fractured femur which shows the extensive comminution so often present in the compound fractures of battle casualties.

time proven methods of surgical care have been neglected. We are inclined to attribute a large portion of the results described to the liberal use of plasma, blood transfusions, and to the treatment of the wounds by the methods outlined in this paper.

PERIPHERAL NERVE INJURIES

Injuries of the peripheral nerves occurred in 53 patients, or 8.3 per cent of the patients who were wounded in the extremities. The radial nerve was the most frequently involved of all peripheral nerves, injuries to it constituting 30 per cent of the peripheral nerve injuries, and it was traumatized nearly twice as often as the ulnar nerve (Table IV). This finding is consistent with the fact that the arm was the most common site of injury, the high incidence of fractures of the humerus, and the known vulnerability of the radial nerve.

In approximately half of the peripheral nerve injuries the loss of function and sensation was not complete. These were classified as cases of partial avulsion or contusion of the nerves. The remainder of the cases were put in the classification of complete avulsion of the nerves.

Thirty-four, or 64.1 per cent, of the nerve injuries were caused by fragments while 19, or 35.9 per cent, were caused by bullets. The nerve injury was associated with a fracture in 19 cases.

In no case were the circumstances suitable for primary nerve suture. Contractures were prevented by the use of splints and casts.

INJURIES TO LARGE VESSELS

In avulsion of an extremity and in severe crushing injuries there is naturally involvement of the large vessels to the part. We were surprised at the small number of patients whose wounds were primarily injuries of the large vessels, however. Undoubtedly, many combatants succumb to hemorrhage before they reach a medical activity, and possibly some of the extremities which had been removed before the patients reached us (Table VIII) were amputated because of vascular injuries.

There were but 9 cases which we could classify as injuries to large blood vessels. The subclavian vein was injured once and, following a secondary hemorrhage, was partially occluded by suture (Table V).

The remaining 8 patients sustained injuries to the vessels of the lower extremity, 4 to the femoral and 4 to the popliteal. In 7 of these patients gangrene occurred, and amputation was inevitable. In one patient, following ligation of the popliteal vein because of hemorrhage, circulation in the foot gradually improved.

Patients with injuries to the large vessels presented individual problems. In some cases the vessels were ligated immediately to control hemorrhage; in others extravasation of blood occluded the vessels and stopped the hemorrhage. It was found that after replacement of lost blood, and control of hemorrhage, amputation usually could be deferred until the formation of a line of demarcation between healthy and nonviable tissue.

We are occasionally asked if suturing of wounds of large blood vessels has been attempted. In the wounds which we have seen, the vessels were damaged considerably, the wound edges were very irregular, the ends of the vessels sometimes were retracted, and the

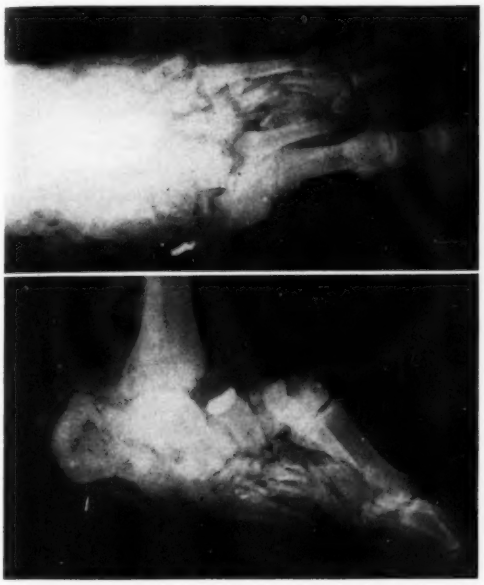

Fig. 3. Roentgenograms of badly mutilated foot which illustrates the extensive damage caused by some missiles. These cases present problems in regard to treatment.

surrounding tissues were edematous and ecchymotic. The possibility of infection was great. In short, more unfavorable conditions for the restoration of the continuity of a blood vessel are hardly imaginable.

The following case illustrates some of the problems encountered.

A private first class, U.S. Marine Corps reserve, aged 21 years, was admitted on February 3, 1944. He had been struck in the left thigh by a bullet on the preceding day. Several hours later a corpsman reached him and administered plasma. More plasma was given at the first-aid station.

Physical examination revealed a large, well developed man who was lethargic and responded poorly. Temperature was 104.4 degrees. Pulse rate was 140 per minute. Respirations were 26 per minute. There was a small wound on the lateral aspect of left upper thigh, a larger wound about 3 centimeters in diameter medial to the femoral vessels. Blood oozed from both wounds. The entire thigh was edematous, ecchymotic, and tense. The left leg and foot were mottled and cold. Pulsations could not be felt in the popliteal, dorsalis pedis, nor in the posterior tibial artery. Examination by means of the x-ray was negative. Erythrocytes numbered 1,770,000 per cubic millimeter of blood. Leucocytes numbered 7,850 per cubic millimeter and the hemoglobin estimation was 6.5 grams per 100 cubic centimeters of blood.

Fig. 4. Roentgenogram of a foot which had sustained gunshot wound in tarsal region.

Two liters of glucose solution and 2 units of plasma were given immediately. Sulfathiazole therapy was started by mouth, and gas gangrene antitoxin was given. A firm dressing was applied to the wounds.

The general condition improved slowly and the ecchymosis, which extended to above the inguinal ligament, began to recede. The lethargy decreased. The left foot and leg became cyanotic to the midleg. Three transfusions of 500 cubic centimeters each were given.

On February 11, 1944, when the patient was dismissed from our care, the temperature was normal, the swelling and ecchymosis of the thigh had disappeared, the wounds were clean and were healing, and there was a definite line of demarcation at the midleg. We felt that amputation could be performed with a greater degree of safety at the conclusion of this period than at any other time.

TETANUS TOXOID AND BACILLUS ANTITOXIN

Although these patients had previously been given a booster dose of tetanus toxoid before they went in combat, it was our policy to give all wounded an additional dose when they came aboard unless one had been given elsewhere subsequent to the time of injury. No case of tetanus developed in this series indicating that toxoid is of value and produces an immunity to tetanus.

Gas bacillus antitoxin was administered as a prophylactic measure to some patients; however, the greater majority did not receive any. Of 7 patients who developed gas gangrene only 1 had been given the prescribed prophylactic therapy. We are unable to draw conclusions concerning the efficacy of the serum from a prophylactic standpoint. Inasmuch as the only cases of gas gangrene that

we encountered were in patients with large, deep wounds, we believe the antitoxin should be given to patients with wounds of that type.

In those patients developing gas gangrene we employed serum in adequate amounts along with various other therapeutic measures, i.e. surgery, chemotherapy, penicillin, and transfusions. Its value as a therapeutic agent could not be determined due to these variables.

PENICILLIN

Our experience with penicillin has been limited. It was used as a therapeutic measure in all cases of gas gangrene, 15,000 units of the drug being given intramuscularly as soon as the diagnosis was made. Every 3 hours thereafter a similar amount was given by the same route until the patient's temperature returned to normal. Because so many agents were used in an effort to control this infection, it would be presumptuous for us to judge the value of penicillin in the treatment of gas gangrene. At the present time it is the adjunct to surgery that holds the most promise.

GENERAL TREATMENT OF FRACTURES

When large numbers of fresh compound fractures are being received it is necessary that the most seriously injured be treated first. Those individuals in shock were given treatment immediately. They were treated by the usual measures before any care was rendered the fracture. While these patients were receiving shock treatment, those individuals with extensive injury to the soft tissue were cared for, as well as those coming aboard whose trauma was of such a nature as to necessitate the application of a tourniquet elsewhere. After these had been operated upon those with less extensive soft tissue wounds were seen.

Wound treatment. The care of the wounds associated with fractures was much the same as has been outlined for soft tissue injury without fractures. In addition, we have removed small accessible pieces of bone or a foreign body if we believed they would interfere with reduction of the fracture. A trimming operation of the wound, thorough cleansing with soap and water (being sure that all injured tracts are washed), followed by massive saline irrigation of the wounds, have given excellent results in our hands. In no instance have we encountered a pyogenic infection of any severity as indicated by the patient's general condition and temperature. We are of the opinion, from our observations of these cases, that time-consuming, massive excision of soft tissues is unwarranted. It is physically impossible to care for patients in this way unless we are to delay the treatment of others who are wounded. Such delay, which would constitute days, might lead to well recognized complications of those wounds not treated early.

Reduction. If possible, reduction of a fracture was accomplished by conservative measures. When necessary, Steinmann pin traction was used to overcome shortening. Pins used were incorporated in a plaster cast in order to maintain satisfactory reduction. All reductions of fractures of the long bones were performed under fluoroscopic control and post-reduction x-ray examinations after the cast had been applied were made to check the position of the fragments.

Immobilization. From our experiences with these cases plaster immobilization has been quite satisfactory and was the method of choice in treating such badly comminuted fractures as were seen in this type of warfare. After a fracture had been reduced properly and immobilized by this medium, the patient was comfortable. Even though the patients were confined to bunks aboard a ship, they could be turned easily. Quite frequently the cast immobilizes a wound which was large and in close proximity to a joint; therefore there was less pain and less likelihood of joint contracture. Some observers believe that aboard ship, fractures of the long bones should be treated by half pin devices in order that, if necessary, the individual may abandon ship more easily and, while in the water, the fractures will be immobilized. We are unable to substantiate such reasoning. We cannot subscribe to the use of these devices because in doing so we would be discarding a proved and satisfactory method of treatment of a compound fracture merely in anticipation of a situation very unlikely to arise. The placing of multiple pins in healthy bone where they will be in close proximity to large potentially

infected wounds is unsound surgery. Contamination of the pin holes might take place, leading to infection of healthy bone. The bones were so extensively comminuted that it was rare to find one fractured in such a manner as to make application of one of the devices possible.

When patients were ambulatory, the hanging cast was used to treat fractures of the midhumeral shaft. In a few instances we have found that correction of overriding of fragments was not accomplished because the cast would become adherent to the wound dressing, thus preventing traction. In order to prevent this we suggest wrapping the dressing with a thin layer of oiled silk. This will prevent soiling of the cast by wound seepage and will avoid adherence of the dressing to the cast.

Potential gas gangrene associated with fracture. It has been our misfortune to encounter 5 cases of malignant gas gangrene which developed in compound fracture (1.85%). In all instances the fractures involved the long bones. There was extensive damage to the soft tissues and severe comminution of the fractures. Treatment of these cases was rendered in the manner outlined. We were impressed with the insidious onset of symptoms suggesting gas gangrene. We are of the opinion that an early clinical diagnosis of gas gangrene was not made due to the insidious onset of infection as well as the fact that a plaster cast prevented examination of the wound and surrounding tissue. Because of the delay in diagnosing this complication, the infection had spread, necessitating high amputation of the extremity. In order to insure earlier recognition of gas gangrene, in compound fractures of long bones with extreme damage to the soft tissues, we recommend in carefully selected cases, a waiting period of 3 days between the débridement and reduction and immobilization. Such treatment should be reserved for compound fracture in which the soft tissue has been extensively macerated. During the interval, the extremity can be maintained in position by a Thomas splint for the lower extremity or a Jones splint for the upper extremity. An earlier diagnosis of gas gangrene can be made, leading to measures which might save an extremity. If amputation is necessary, the site of operation might be a low one, affording a more satisfactory prosthesis.

AMPUTATIONS

In this series 34 amputations were performed; 70.5 per cent were necessary because of irreparable damage, 17.6 per cent for gas gangrene, and 14.7 per cent for vascular injury. In Table VII is listed the site of amputation with the number for each part. Also is listed the indication for amputation.

In the battlefield a guillotine type of amputation may have its indications; otherwise such a procedure is unjustified. If the amputation is performed at a medical unit where an anesthetic can be given and where shock can be treated, preferably before the operation is done, we believe a flap type of operation to be the one of choice. The additional short time required in doing this operation is not a contraindication, for the patient can receive the same shock care on the operating table as he would in bed. Skin flaps should be left open and no sutures placed in the fascia, if the operator believes they should be left unsutured because of infection or potential infection of the stump. There is no logical mechanical or physiological reason to lead one to believe that two skin flaps afford an opportunity for infection to locate in the stump. After a few days, if the open stump is clean, a secondary suture of the fascia and skin can be done in a short period of time. It is our opinion that nothing is lost by performing amputations with flaps. The many secondary complications resulting from a guillotine operation, i.e., osteomyelitis, conical stump requiring plastic procedures, and reamputation, would be avoided.

COMPLICATIONS

Infection. Pyogenic infection was present in the wounds of 4.3 per cent of patients as determined by inspection of the wound and the systemic signs of infection. In no case was there a spreading pyogenic infection. It would have been of academic interest to culture all wounds, but this was not practicable and would hardly have altered the treatment (Table IX).

TABLE IX.—COMPLICATIONS

	No. patients	Well or improved	Died
Grossly infected wound, mild	28	28	
Secondary hemorrhage	3	2	1
Gas gangrene	7	5	2
Thrombophlebitis	1	1	
Pulmonary embolism	1		1
Pleurisy	1	1	
Pneumonia	1	1	

Note: Does not include concomitant conditions such as hemothorax, pneumothorax, intracranial injury, etc.

Secondary hemorrhage. In 3 patients secondary hemorrhage, one of the most dreaded of all complications, occurred. In 2 patients the hemorrhage was controlled by ligation, blood and plasma were administered, and the patients recovered. One patient, with a large, infected wound of the popliteal space which had been previously packed in another facility, had a secondary hemorrhage during the night which was controlled only after he had become nearly exsanguinated. After his condition improved and while preparations were being made for operation there was another massive hemorrhage. It was necessary to amputate in order to control the bleeding. The patient died suddenly of collapse.

Gas gangrene. There were 7 cases of gas gangrene, an incidence of 1 per cent in 638 patients. Plasma, transfusions, penicillin, sulfonamides, multiple incisions, and amputation were employed in combating this serious infection. There were 2 deaths, a mortality of 18 per cent. In one group of patients who were wounded while in the water or immediately after going ashore, there were no cases of gas gangrene. One patient who developed gas gangrene was wounded aboard ship; 6 patients were wounded while fighting on land.

Miscellaneous. Phlebitis, pulmonary embolism, pleurisy, and pneumonia were seen once each as a complication of wounds of the extremities.

Deaths. In this group of 638 patients who had been wounded in the extremities there were 8 deaths, a mortality of 1.2 per cent. In 5 cases the patients were *in extremis* on admission and died a short time after being brought aboard. One of these patients had gas gangrene infection of the arm which had extended to his chest wall. The 4 other patients had extensive multiple injuries, including thoracic wounds, fractures of the skull and traumatic amputation of multiple extremities, which were complicated by profound shock.

Of the 3 remaining patients, all of whom were under our care for more than 1 day before death, 1 died of a pulmonary embolus, 1 of gas gangrene of the leg, and 1 succumbed following massive secondary hemorrhages. In this series the mortality rate of patients with wounds of extremities who survived the first day aboard ship was 0.4 per cent.

Statistics in regard to the mortality of wounds of the extremities sustained in battle are not readily available. As a basis of comparison and as a commentary on the progress of surgical care, it is interesting to recall that, according to Boehler, in World War I the average mortality rate of fractures of the femur was 50 per cent and that in the Crimean War the mortality rate of gunshot fractures of the femur was 96 per cent; the remaining 4 per cent were amputated.

SUMMARY AND CONCLUSIONS

1. Of 984 patients wounded in amphibious warfare 64.8 per cent sustained wounds of the extremities.

2. The majority of extremity wounds were caused by fragments from shells, bombs, or grenades. Wounds inflicted by thermal agents, bayonets and swords constituted a small percentage of the total.

3. Wounds of the extremity varied from minute puncture wounds to large avulsions. Seventy-two and five-tenths per cent of the patients had deep wounds.

4. The lower and upper extremities were equally involved. The upper arm was the area most frequently injured. Twenty-six and forty-eight hundredths per cent of patients received wounds of this region. The hand was injured out of proportion to its size.

5. The peripheral nerves were injured in 8.3 per cent of patients with extremity wounds. The radial nerve was most frequently injured.

6. The incidence of injury to the large blood vessels was surprisingly small. Conditions favorable for suturing torn blood vessels were not encountered in this group.

7. Thirty-six per cent of patients with extremity wounds sustained fractures. Ninety-

one per cent of the fractures were compound. Nearly all fractures were extensively comminuted.

8. Shock and hemorrhage were treated and controlled before definitive treatment was performed. Ten per cent of patients required immediate treatment for these conditions. Transfusion of whole blood was the most valuable measure in the treatment of shock associated with hemorrhage.

9. Conservative but thorough débridement, cleansing of the wound with sterile water and soap, and adequate irrigation of all tissue planes with normal saline solutions, followed by placing of vaseline gauze in the wound has proved to be a satisfactory method in caring for war wounds of the extremities.

10. Foreign bodies should not be removed in fresh casualties, except when accessible, or when their presence interferes with the reduction of a fracture, or when they are pressing on large blood vessels or upon nerves.

11. The treatment outlined for soft tissue wounds has given satisfactory results when used in wounds associated with fractures.

12. Reduction of fractures should be accomplished by as conservative means as possible. In general, plating of fresh war fractures is contraindicated.

13. Plaster immobilization, with incorporated pins when necessary, is a satisfactory method of treating these fractures. In carefully selected cases of fractures of the long bones with extensive soft tissue injury in which muscle is macerated it is advisable to delay for 3 days cast immobilization in order that the injured part can be examined for the development of gas gangrene.

14. The guillotine operation should be reserved primarily for those cases in which speed is a prerequisite. Where the facilities of a complete hospital are afforded, the flap type operations, with delayed closure if necessary, are recommended.

15. Pyogenic infection occurred in 4.3 per cent of patients with extremity wounds. In this series no serious infection from this cause was encountered.

16. Gas gangrene developed in 1 per cent of the patients with extremity wounds. The mortality rate from this condition was 18 per cent.

17. The mortality rate of all patients with extremity wounds who survived the first day aboard ship was 0.4 per cent.

SKIN GRAFTING AND SECONDARY CLOSURE IN WAR WOUNDS

A Preliminary Report

CHARLES S. WHELAN, M.D., F.A.C.S., Captain M.C., A.U.S., Worcester, Massachusetts, and
WESLEY D. THOMPSON, Jr., M.D., F.A.C.S., Major, M.C., A.U.S., Philadelphia, Pennsylvania

THE treatment of war wounds may be divided into three periods: the early, the convalescent, and the late period. During the early period hemorrhage is controlled, foreign bodies are removed, and débridement is accomplished. The excellent condition of the majority of the battle wounds coming to us is proof that this phase of treatment is being well performed. The convalescent period concerns itself with closure of the wound and restoration of function. The late period is limited to certain wounds which, months or years later, require reconstructive procedures to improve function or to correct cosmetic defects. It is the second, the convalescent period, with which this study is concerned.

Adequate treatment of war wounds during the convalescent period offers many problems. If they are allowed to close spontaneously, not only is much time consumed but deforming scars may result.

From July 12, to October 31, 1943, inclusive, of patients admitted to the surgical service, 967 were battle casualties. During this period 145 plastic procedures were performed, practically all of which were on wounds of the extremities. Of these procedures 81, or 56 per cent, were secondary closures and 64, or 44 per cent, were skin grafts. Relatively few of these operations were done during July and August as the hospital during the Sicilian campaign was serving as an evacuation hospital. During the first week of the Italian campaign we were authorized to make a study of the efficacy of early skin grafting and secondary closure of wounds. Consequently, 140 of the 145 procedures were performed during September and October.

Shortly after the beginning of this study a mimeographed form was utilized for keeping detailed record of each case. Such a record has been completed on 97 patients, representing 114 plastic procedures on a total of 144 wounds. It is upon this latter group that this report is based.

TABLE I.—PLASTIC PROCEDURES, JULY 12 TO OCTOBER 31, 1943, INCLUSIVE

	Secondary closures	Skin grafts			Monthly totals
		Split thick	Full and flap	Reverdin	
July	1	0	0	0	1
August	1	3	0	0	4
September	15	6	3	2	26
October	64	43	3	4	114
Totals	81	52	6	6	145

GENERAL CONSIDERATIONS

Most of these cases were battle casualties; only 5 were not traumatic in origin. Forty-eight patients were injured by shell fragments, 15 by bullets, 2 by mine explosions, 1 by grenade, and 11 were injured in accidents. The type of missile was not stated in 11 cases. One hundred and twenty-five of the 144 wounds, which are being reported in detail, were wounds of the extremities. The others were: gluteal, 11; chest wall, 3; genitals, 2; abdomen, back, and perineum, 1 each. Eighteen, or 13 per cent, of the wounds treated were associated with compound fractures. This number does not include phalangeal fractures.

Previous treatment. Débridement had been done in 63 cases before arrival at this hospital; in 16 cases dressings only had been done; 16 had had amputations. Only 1 patient in this series entered with a fresh wound.

Time interval. In the 97 cases an average of 4.9 days had elapsed between injury and admission to this hospital. An average of 19.5

days elapsed between injury and plastic operation.

Treatment of the wound. The wound was inspected upon arrival at the hospital. If necessary a toilet of the wound was done which consisted of the removal of all necrotic elements. Continuous aqueous azochloramid was started and continued until the wound appeared sufficiently clean. For at least 48 hours before the skin graft or secondary closure continuous dressings of hot boric acid solution or normal saline were used. The wound overlying a compound fracture was treated in much the same way through a window in the cast. Bacteriological studies were not done as it is well known that all of these wounds are contaminated. The plastic procedures were done when the wounds appeared to be surgically clean.

Size of wounds. To determine accurately the size of the wounds, metal rulers were incorporated in the operating setup. It is surprising how much one can err in estimating the size of a wound. The largest area grafted was a third degree burn, comprising slightly more than 90 per cent of a lower extremity. The smallest was a 1 by 1 centimeter wound of the wrist on which a split thickness graft was placed.

Special considerations. Foreign bodies were present in the immediate vicinity of wounds in 9 instances. The bone was exposed in 14 wounds and tendon was exposed in 7.

Type of operation. Fifty-six, or 49 per cent, of these 114 operations were secondary closures, 54, or 47 per cent, were skin grafts, and 4, or 4 per cent, were combinations of the 2 procedures.

Anesthesia. Local anesthesia was used more often than any other, having been employed 53 times. Spinal anesthesia was used for 34 procedures, pentothal for 15, and ether for 12. In general, local is the anesthetic of choice in the treatment of smaller wounds. The graft is taken after intracutaneous infiltration, the orange-peel effect from the distention of the skin making it relatively easy to cut the graft. We feel that a razor blade held in a straight clamp is the best instrument for taking the smaller grafts. The thigh need not be the donor site as any convenient area of skin on the extremity or the trunk may be utilized.

Sulfanilamide. No delay has been noted in the healing of wounds nor has there been any interference with take of the graft in those cases in which sulfanilamide crystals were used locally. We feel that it should be employed routinely.

Immobilization. No form of immobilization was deemed necessary in 61 instances. Plaster-of-paris was used 35 times; splint, 9 times; sling, 5 times; ace bandage, 3 times, and adhesive strapping, once. Molded plaster is a most convenient agent for immobilization in plastic procedures on the extremities. Grafts and closures were frequently done through a window in the cast if removal of the existing cast was deemed inadvisable. For shoulder and arm wounds, a double sling is most effective.

SKIN GRAFTING OF WOUNDS

Excision of margins. The margins of recipient areas were usually not excised prior to grafting. Exceptions were made in indolent wounds with unhealthy edges.

Donor site. The anterior surface of the thigh was used most frequently as the donor site. The posterior surface was used when the wound to be grafted was located on the posterior aspect of the lower extremity. When very large grafts were necessary, the abdomen, chest, or back were utilized.

Drainage. Wounds with draining pockets or sinuses received special attention. The pocket or sinus was drained either through a rent in the graft or to the side of the graft. One of the authors preferred wet dressings to the vaseline dressings. The dressings were kept continuously moistened by aqueous azochloramid or boric acid solution injected through a Dakin's tube incorporated in the dressing. These grafts were generally dressed and the drain removed in 2 to 4 days. The moist dressings were continued for 7 to 10 days after operation. The aqueous azochloramid did not seem to injure the grafts. In an occasional case blistering of the normal skin was encountered. The end-results were the same whether the moist or the routine vaseline gauze dressings were employed.

Wounds were not drained simply because of irregularities on the surface of the recipient area. In these vaseline gauze was molded into

the depressions, over which fluffed gauze was placed to aid in maintaining even pressure throughout the grafted area.

Drainage was instituted in the grafted cases 12 times, and no drainage was used in 45 wounds. None of the four wounds treated by the combination of graft and closure was drained.

Suturing of grafts. The grafts were most often sutured in place, first by anchor sutures of No. 0000 Deknatel silk, followed by continuous suture around the graft. Some thin split thickness grafts may do well without suturing.

Pressure. The necessity for even pressure over the grafted area cannot be overstressed. Mechanics' waste is an excellent substitute for sea sponge, if care is exercised to fluff it well to remove its lumpiness. It is advisable in extremity dressings to apply a wad of waste on the side of the limb opposite the dressing to produce an equalized pressure on the limb, thereby avoiding undue pressure on vessels and nerves. The pulse should be checked distally after the application of a snug bandage to the extremity.

Instrument. The Padgett dermatome was employed 25 times; the Ferris Smith skin graft knife and the razor blade were used 15 and 9 times, respectively. The dermatome was used in all instances in which large defects were covered. The razor blade is excellent for cutting a strip to fill the granulating area of a long narrow wound.

Complications. There was infection of the recipient area in 3 cases and in 2 there were mild infections of the donor site. Scarlet fever occurred in 1 of our grafted patients and the graft failed to take.

Postoperative dressings. With the exception of those cases in which drainage had been instituted in the recipient area, these wounds were not dressed sooner than 7 days following operation, as a rule. In very large areas or in grafts of amputation stumps, the wound was not disturbed for 2 weeks or longer.

The further we went in this work, the less we tended to be discouraged by the appearance of some of the grafts at the end of a week or 10 days. Some areas, which at that time seemed to have relatively little take, were completely healed in 21 days. The explanation obviously is that certain areas which appear to be unsuccessful are in reality covered with a very thin epithelial layer

Results in skin grafts. We have arbitrarily chosen 21 days as the time at which an estimate should be made of the extent of the take of the graft or the percentage of healing in wounds secondarily closed. Any area that had not healed by that time was considered a failure.

TABLE II.—PERCENTAGES OF TAKE OF SKIN GRAFTS (79 wounds)

	Cases	Per cent
75 to 100 per cent	51	68
50 to 75 per cent	12	16
25 to 50 per cent	2	3
0 to 25 per cent	10	13

SECONDARY CLOSURE OF WOUNDS

The nature of the wound is the most important factor in deciding whether a skin graft or a secondary closure should be performed. Lacerated wounds in which the edges are not too far apart or penetrating wounds in which there has not been appreciable loss of tissue do well with secondary closure. Wounds in which there is considerable separation of the skin and wounds in which the granulation tissue lies at or near the surface of the skin are more amenable to skin grafting. Small lacerated wounds often heal promptly by the use of adhesive approximation.

Fifty-six, or 49 per cent, of the 114 plastic procedures were secondary closures.

Prior to secondary closure the same preoperative management of the wound was followed as in the skin graft cases. The edges of the skin were in most instances trimmed and a slight toilet of the wound was done if indicated. The choice of suture material did not seem to make a great deal of difference, provided undue tension was avoided. Equally good results were obtained with wire, silk, and silkworm gut.

Immobilization is as important after secondary closure as it is after skin grafting. Drainage was instituted in secondarily closed wounds if dead space remained beneath the coapted margins. Twenty-five, or 42 per cent, secondary closure wounds were drained and

34, or 58 per cent, were closed without drainage. Infection occurred postoperatively in only 3 wounds.

TABLE III.—PERCENTAGES OF HEALING IN SECONDARY CLOSURES (77 wounds)

	Cases	Per cent
75 to 100 per cent	55	71
50 to 75 per cent	8	10
25 to 50 per cent	2	3
0 to 25 per cent	12	16

The apparent discrepancy in the number of wounds is attributable to reoperation in a small group

The results in the 4 wounds, in which a combination of skin grafting and secondary closure was used, are: 3 wounds, 75 to 100 per cent; 1 wound, 50 to 75 per cent.

PLASTIC PROCEDURES ON WOUNDS ASSOCIATED WITH COMPOUND FRACTURES

Skin grafts. Eleven split thickness skin grafts were placed on wounds associated with compound fractures. Phalangeal fractures are not included. The compound fractures were located as follows: metacarpals, 3; tibia, 2; fibula, 2; radius, 1; ulna, 1; femur (internal condyle), 1; and metatarsals, 1. These wounds averaged 9 centimeters by 5.5 centimeters. The largest wound was 15 centimeters by 11 centimeters associated with a compound fracture of the tibia in which there was considerable loss of bony substance. Bone was exposed in 6 of the cases. In these cases the grafts took over bone where the periosteum was intact. Bony spicules protruding through the graft were removed with the rongeur. If a draining sinus was present, a rent was made in the graft and a rubber tissue drain was inserted through it into the sinus. The average take of these grafts was 78 per cent.

Secondary closures. Secondary closure has been performed on 7 wounds over compound fractures. The fractures involved the following bones: scapula, 2; femur (greater trochanter), 2; fibula, 2; and metatarsals, 1. These wounds averaged 8.6 centimeters by 4 centimeters, the largest being 16 centimeters by 8 centimeters. Rubber tissue was used where drainage was indicated. The average healing of these wounds at 21 days was 80 per cent.

OBSERVATIONS

A comparison can hardly be made of the results of skin grafting and secondary closure since in most instances these procedures are used in different types of wounds. As this study progressed we tended to treat more wounds by skin grafting than by secondary closure. Covering large granulating wounds with "skin dressings" offers definite advantages. By sealing the wound the element of infection is eliminated and the tissues are allowed to return more promptly to a normal state.

These plastic procedures seem to promise a shortened period of disability for patients with compound fractures. Skin coverings over their wounds keep out infecting organisms which would continue to gain access through an open wound. In cases in which indicated, reconstruction operations may be done at an earlier date. Plastic procedures on these wounds do not increase the period of hospitalization because these patients are already under prolonged treatment for their fractures.

In dealing with war wounds, especially the larger ones, one cannot strive for the ultimate in cosmetic result.

Reverdin grafts, although not advisable as routine procedure, should not be totally discarded. They have, we believe, their particular place in bridging over those last few millimeters of wound. It is suggested that these grafts be taken from the immediate vicinity of the wound, where the tissues are already more or less disfigured.

Certain parts of the body have been found to be resistant to plastic procedures. The most recalcitrant area has been that overlying the tibia. Also one is apt to have difficulty with wounds of the sole of the foot, the buttocks and the shoulders.

Plastic procedures in our experience have failed more often in small circular wounds than in larger ones. We could not attribute this to the presence of foreign bodies or any other factor. The reason for the poorer results in the small wounds is not clear.

Occasional patients are encountered in whom, for some unknown reason, both skin grafting and secondary closure are repeatedly unsuccessful.

Thin split thickness grafts seem to be surer of take than thicker ones. If there is reasonable doubt of a successful take in a given wound, it is well to apply a thin graft. Thicker grafts should be placed over pressure points. Full thickness grafts were successful in the palm of the hand.

CONCLUSION

We are of the opinion that skin grafting and secondary closure are eminently worth while in the treatment of war wounds. The period of hospitalization is definitely shortened. Many patients, who otherwise would be lost through evacuation, will be returned to duty. Patients with severe wounds of the soft tissues and those with compound fractures are rendered more comfortable. By these plastic procedures the underlying tissues are sooner restored to normal and patients are earlier prepared for any reconstructive procedures that may be necessary in the Zone of the Interior.

THE EFFECTS OF ORCHIECTOMY ON PRIMARY AND METASTATIC CARCINOMA OF THE BREAST

NORMAN TREVES, M.D., F.A.C.S., JULES C. ABELS, M.D., HELEN Q. WOODARD, Ph.D., and JOSEPH H. FARROW, Lieutenant Commander, M.C., U.S.N.R., New York, New York

FOR over two score years there has been an increasing interest in the effects of oophorectomy on mammary carcinoma, both primary and metastatic. For more than half of that period the medical literature on radiation therapy has seen a substantial increase in the bibliography on radiation castration for metastatic breast cancer, more especially as regards the effects of such a procedure on the secondary deposits in bone. The encouraging regressions of the skeletal metastases from mammary carcinoma following castration in women, still menstruating, have suggested the possibility that orchiectomy might retard or even cause regression of mammary cancer in the male—both in the primary and metastatic lesions. The latter experiment was begun more than 2 years ago at the Memorial Hospital and was noted in a preliminary report 4 months after the first patient was orchiectomized. Because of that result other cases for such therapy by surgery have been collected.

In 1942 Farrow and Woodard (10) were led to observe the effects of the administration of androgens and estrogens on the serum calcium in patients with skeletal metastases from breast cancer. Impressed by the favorable results obtained in the retardation of the growth of osseous metastases in mammary carcinoma by radiation castration they studied the effects of "chemical castration" by the injections of testosterone propionate. They found that the 3 patients who received such therapy had developed increased blood calcium levels as well as an increased output of calcium in the urine. The chemical changes were accompanied by clinical and roentgenographic evidence of increased activity in the metastatic disease in bone. The administration of estrogens was found to produce a similar effect. They inferred, therefore, that the ability of the male and female sex hormones to cause hypercalcemia in such cases was due to the stimulation by the hormones of the growth of the metastatic tumor. However, this finding is at variance with the observations of Dobriner and of Abels (1) who administered to each of 2 patients a total of 3 grams of both crystalline testosterone and testosterone propionate without producing a stimulating effect on the primary or metastatic disease or increasing significantly the calcium level of the blood.

The observations that the use of androgens and estrogens in women with breast carcinoma was deleterious, the numerous favorable results in inoperable and metastatic carcinoma produced by x-ray castration and the older reports on surgical castration for inoperable breast cancer, suggested that castration be tried in males. Farrow and Adair (9) observed the results of orchiectomy on osseous metastases from breast carcinoma. Their patient has been reported previously, but only 4 months after operation, and is the first of the 6 subjects in the present communication. Enough time has now elapsed to evaluate fully the overall effects of orchiectomy. At the time orchiectomy was performed the clinical classification of the 6 cases under report was primary operable, 1; prophylactic, 1; recurrent inoperable, 1; primary inoperable, 3.

The consent for orchiectomy, even in the elderly male with advanced breast cancer was most difficult to obtain. It appears to be a triumph of medical persuasion to obtain permission for this operation. Even an elderly male with the intense pain from osseous metastases was unwilling to undergo castration. The female who in her psychological make-up expects the climacteric at one time or another is more easily persuaded to submit to oophorectomy than is the male who rarely, if ever, expects a complete cessation of his

From the Breast Department, the Clinical Metabolic Laboratories and the Chemistry Department, Memorial Hospital, New York.

sexual functions. It seems to be more difficult to obtain permission for castration in males suffering from mammary cancer than in malignant disease of the prostate.

CASE REPORTS

The following case reports have been fully abstracted and have been chronologically listed in the order of the dates of their castrations.

CASE 1. M. S., a white male, aged 72 years, was admitted to the Breast Clinic of Memorial Hospital on April 28, 1941. He was an Italian Catholic, married, and the father of two children. He had noted a mass in his left breast which had ulcerated 4 months prior to the date of his application for treatment.

On physical examination the patient, in fair general condition, did not appear to be 72 years of age. His full head of brown hair was only slightly streaked with gray. A sloughing ulceration destroyed the left nipple and areola. The edges of the lesion were rigid and umbilicated. The crater measured 3 centimeters and was partly filled with a moist, grayish slough. Underlying the ulcer was a stony hard mass 5 by 6 by 2 centimeters. The tumor was movable over the chest wall. The axilla contained several firm, metastatic nodes. The genitalia were normal. Biopsy of the tumor was not obtained at the time. The x-ray examination of the lungs and thoracic cage was negative for metastases.

It was most difficult to obtain the patient's cooperation in initiating treatment and he ignored all requests for his return to clinic until 10 months following his initial examination (February, 1942).

Re-examination on February 5, 1942, revealed an extension of the primary lesion (Fig. 1). It was still movable over the chest wall. The nodes in the axilla had increased slightly in size and one small node could be palpated in the left supraclavicular fossa as well as the right cervical region. In addition to the original symptons he now complained of pains in the chest and dorsal spine.

X-ray examination was made February 6, 1942, of both shoulder girdles, skull, lower ribs, lumbar spine and pelvis. There are many areas of osteolytic bone destruction involving particularly ribs (Fig. 3), 4th lumbar vertebra, numerous areas in the pelvis and upper femora (Fig. 4). Two osteolytic areas were seen in the skull and one in the upper portion of the left humerus. Both scapulae were involved. Conclusions: Carcinoma metastases to bone widespread, osteolytic type.

Because of the extension of the disease and the positive evidence of osseous metastases the patient's clinical classification was changed to primary inoperable and he was admitted for orchiectomy.

At operation a formal incisional biopsy specimen of the breast lesion was taken and bilateral orchiectomy was done February 9, 1942. The testes were removed in the routine fashion under infiltration anesthesia with 1 per cent novocain. A wedge biopsy specimen was removed from the primary breast lesion. The patient was discharged from the hospital on the 10th postoperative day.

Pathological report: The testes showed atrophy and interstitial cell hyperplasia. The report on the biopsy tissue from the breast tumor was: "Infiltrating mammary carcinoma grade II."

The patient was observed 2 weeks after the operation. He reported marked relief from the pain in the skull, ribs and spine. Slight regression was noted in the size of the mammary lesion but the red color in the surrounding skin had definitely faded. One month later regression was noted in the axillary disease. Three months later relief from the pain had become marked and the lesion appeared drier and smaller (5 by 3 by 1.5 cm.). He complained of *hot flashes* and *profuse sweating*. Clinical observation, almost continuous, for 28 months after orchiectomy showed continued regression in the primary lesion which had been replaced by a cicatrix. The last x-ray examination showed some questionable areas of reactivation of the metastatic disease in bone. This finding may be significant since the alkaline phosphatase, which had been normal since the initial rise which usually occurs immediately after orchiectomy, now showed a slight elevation (from 3.8 to 5.5 units).

Reports on subsequent x-ray examinations: March 13, 1942, Carcinoma metastases to bone widespread, showing further advance in the skull and no evidence of calcification.

May 28, 1942, films of this day, when compared with the previous views, do not reveal any well marked changes. However, some of the pathological fractures in the ribs have become united with considerable callus production. The number and extent of the areas of bone destruction or metastases apparently has not increased and it appears that the progress of the disease has at least been arrested.

June 22, 1942, the changes previously described are again seen. Continued slight improvement has occurred in all of these areas of bone destruction previously noted. This improvement is characterized by further calcification in the previously osteolytic sites. There does, however, appear to be a slightly greater pleural thickening at the left base than before and now an ill defined nodular densification is present in the left intraclavicular region that may represent early cancer metastases to the parenchyma. Conclusions: carcinoma metastases to bone, widespread, showing continued reparative change as described previously.

May 25, 1944, examination of the cervical spine, anteroposterior and lateral views showed the spinous process of the second cervical vertebra to have a large cystic area involving the posterior aspect. The remainder of the vertebrae showed decalcification but no definite evidence of a destructive process. This change, noted in former examinations, ap-

parently is not progressive. The areas of decalcification previously described in the skull films, in the frontal and occipital regions, are unchanged. The pelvis and upper femora likewise show no interval change. There is some destruction of the 12th dorsal vertebra with compression and some osteogenic reaction in this vertebra and possibly the 11th. The lumbar spine, while showing generalized decalcification, shows no definite destructive process.

This case represents a satisfactory and dramatic regression of a primary carcinoma of the male breast which had metastasized to bone. The breast cancer was replaced by a cicatrix (Fig. 2), the metastatic nodes regressed. The secondary deposits, as demonstrated in repeated x-ray films, showed reparative change. The repair in the ribs (Fig. 5), shoulder girdle and spine were striking (Fig. 6). Whether the repair process was one in which new bone replaced metastatic deposits, it is impossible to say—only a formal biopsy would settle this question. The changes in the skull, while showing early regression, now show a diffuse haziness. One cannot say whether this is a sign of activity or bone change due to a deranged metabolism produced by orchiectomy. One reason for looking upon the recent skull changes as possible renewed activity of the metastatic process is the corresponding slight, but definite, rise in alkaline phosphatase.

CASE 2. J. S., a retired sea captain, of Protestant English ancestry, was 75 years of age when first examined in the breast clinic at Memorial Hospital on June 10, 1941. He was married and had reared 6 children. A painless lump had been noted in the right breast 1 year prior to admission.

Physical examination revealed a well preserved white male. The examination was negative except for the breast tumor and an enlarged liver. The right breast, including the nipple was the seat of an ulcerating carcinoma which measured 6 by 4 centimeters. It was movable over the chest wall but there was a suggestion of beginning fixation. The corresponding axilla contained metastatic nodes. The external genitalia were apparently normal. The case was classified primary, operable.

X-ray examination of the chest, June 13, 1941, was essentially negative.

Medical consultation: The enlarged liver was probably due to cirrhosis. There was a history of considerable ingestion of alcohol for 40 years. The laboratory findings, however, were only slightly abnormal as evidenced by (1) an abnormal bilirubin, 1.2 milligrams; (2) a low prothrombin level of 81 per cent; (3) mild macrocytosis.

At operation July 7, 1941, a right radical mastectomy was done. The patient was discharged from the hospital on the 11th postoperative day.

Pathological report: Infiltrating duct carcinoma grade III. Multiple node metastases.

The patient received a routine postoperative x-ray cycle (2000 r to an anterior and posterior axillary port and 1750 r through the axilla direct). Seven months after the radical mastectomy a nodule was noted in the skin over the left occiput and an x-ray film showed metastatic disease in the skull (February 26, 1942). Orchiectomy was advised and refused. Chemical studies of the blood showed no significant change. The patient continued free of distressing symptoms for 4 months, refusing orchiectomy for this reason. He agreed to receive treatment with estrogens and entered the hospital for this therapy. Between July 23 and August 18, 1942, he received 19 doses of 12,000 units of progynon (228,000 R.U.). Following the administration he showed clinical and chemical evidence of hypercalcemia. The lesion in the scalp increased in size; the patient complained of skeletal pain; the breast tissue in the opposite side became tender and thickened; cutaneous nodules appeared on the forehead. Later he complained of nausea, which may have been due to the cirrhosis of the liver but may have been produced by an altered calcium metabolism. In December, 1942, dyspnea was evident and a thoracentesis removed 600 cubic centimeters of light, straw colored fluid. In January, 1943, when the patient's symptoms were numerous and discomforting he consented to bilateral orchiectomy. For the purpose of this report he was reclassified as recurrent inoperable carcinoma.

Examination on readmission showed the patient's general condition to be poor. There were multiple nodules in the scalp, evidence of progression in the diffuse skeletal metastases, and a right hydrothorax.

At operation on January 1, 1943, bilateral orchiectomy under infiltration anesthesia of 1 per cent novocain was carried out.

The patient expired suddenly early on the 3d postoperative day. Permission for examination after death could not be obtained.

This patient was an elderly male in fair general condition, but with probable hepatic cirrhosis. His breast lesion, while advanced, was considered operable in spite of the ulceration. Seven months after operation a nodule was noted in the scalp over the left occiput. X-ray films showed associated destructive areas in the skull. The alkaline phosphatase was elevated from 5.4 to 9.9 units. His death, while not directly due to the operation, was probably hastened by his poor physical condition due to the associated disease.

CASE 3. B. D., a 65 year old butcher, married, the father of one child, and a Jew of Austrian descent, had his initial examination in the breast clinic at the

Memorial Hospital on April 13, 1942. Fifteen years prior to his admission, a painless mass was excised with the right breast. Six months later four radium treatments were given over the operative site. Until December, 1941, he remained free of disease. At that time swelling was noted in the right axilla. On February 25, 1942, the right axilla was dissected. He was referred to the Memorial Hospital for further therapy.

Physical examination revealed a rather obese, full chested, white male in apparent good health, with a well healed, old transverse scar over the right chest wall, 8 centimeters in length. A recent granulating scar extended vertically from the apex of the axilla to the previous incision. There was the usual postoperative reaction in fat but there was no evidence of disease. The heart and lungs were essentially normal. There were no spinal deformities but slight tenderness could be elicited on pressure over the 8th dorsal vertebra. The genitals appeared normal.

Pathological report: While the report on the submitted slide from the axillary dissection was given as: "Alveolar carcinoma. No distinguishing features indicative of origin." A further report from the axillary dissection gave the following information: "Infiltrating duct carcinoma grade II. This does not look like a node metastasis; more like a second axillary primary (assuming that this tissue is from the second operation)."

The films made at the time of his admission to the clinic were reported as follows:

May 27, 1942. Views of the spine show some irregularity in the density of the body of the 12th dorsal vertebra and 3rd and 4th lumbar vertebrae, and of the 1st dorsal vertebra also, with some irregular destruction in the proximal end of the first rib on the right side and the transverse process of the vertebra. Changes noted probably represent carcinoma metastases.

However, because of persistent pain retake studies were made and reported on as follows:

August 28, 1942. Dorsal, lumbar spine and pelvis, further examination: There has been practically no change in the appearance of the previously described metastases, except that there may be slight further compression of the 12th dorsal, and the 1st lumbar also appears to be involved (Fig. 7). The 3rd and 4th lumbar vertebrae are not well demonstrated on the present films. No other areas of metastases are seen. Conclusions: Carcinoma metastases to bone, showing slight increase in the interval, as described here.

The alkaline phosphatase in August 1942, was 4.8 units. While castration had been advised in June, 1942, it was not until April, 1943, that he would submit to the operation. At that time the pain in his back was so intense that he sought relief. The alkaline phosphatase had risen to 6.6 units.

At operation, May 8, 1943, a bilateral orchiectomy was done under pentothal and local infiltration with 1 per cent novocain. The patient was discharged from the hospital on the 6th postoperative day.

Pathological examination of the gonads showed "mild atrophy."

The patient had prompt and almost complete relief from pain. The alkaline phosphatase 2 months later was 3.7 units and 3 months ago (February, 1944) was 2.6 units. At that time x-ray "Views of the spine when compared with previous views reveal evidence of some bone regeneration."

This case represents a very satisfactory clinical result. The patient has been relieved of his pain, and has maintained his good physical condition. The phosphatase level has returned to normal and the x-ray studies show evidence of bone regeneration (Fig. 8).

CASE 4. A. I., an Irish Catholic, 64 years of age, applied on June 1, 1943 to the tumor clinic of the Meadowbrook Hospital for the treatment of a breast tumor. He was the father of one child. The patient's past history was negative except for the presence of a bilateral hydrocele of 3 years' duration.

Physical examination revealed a well developed and well preserved white male, with a firm mass in the lower outer quadrant of the left breast about 3 centimeters in diameter. There were no skin nor nipple changes. The axilla contained no palpable nodes. The genitalia seemed normal except for the slight atrophy usually found in a male of this age and for the presence of bilateral hydroceles each about 5 centimeters in diameter.

Operation was performed June 12, 1943 under general anesthesia (gas-oxygen and ether) and the tumor in the left breast was excised. It was not examined in the operating room. The hydroceles were repaired by excision, the procedure being simplified by doing a bilateral orchiectomy. Convalescence was uneventful, the patient leaving the hospital on the 6th postoperative day.

Pathological examination: Adenocarcinoma of the breast; bilateral hydroceles; normal testes.

The patient was examined 10 days after operation. The incision in the breast was well healed. The scrotal scars were slightly indurated. It was decided that in view of the problem in hand it would be well to rest on the excision of the breast cancer to see if orchiectomy would prevent recurrence or metastasis. For this reason the patient was examined at monthly intervals. In October, 1943, a node was noted in the right axilla (opposite side) and in December this finding was bilateral. A film of the chest revealed no areas of pulmonic or osseous metastasis. The node in the right axilla disappeared but the one on the affected side remained and increased in size. On April 25, 1944, a left radical axillary dissection was done under general anesthesia. The node was a hyperplastic crescent of lymphoid tissue surrounding a lobule of fat. There was no evidence of metastatic disease in the axilla.

This patient has remained free of local or distant disease following the *local excision* of a

Fig. 1. Case 1. Condition of the primary lesion in the left breast at the time of formal biopsy and orchiectomy. This is an extensive ulcerating lesion with associated involvement of axillary nodes.

Fig. 2. Case 1. Condition of the primary tumor 27 months after operation. The ulceration at this time has completely healed, and the lesion has been replaced by a cicatrix.

carcinoma of the left breast. The only adjuvant therapy was the orchiectomy which at the time had not been planned as a therapeutic measure but for the relief of a bilateral hydrocele. The result is most satisfactory 1 year after treatment.

CASE 5. E. S., a 39 year old male of Irish Catholic ancestry, appeared in the breast clinic of Memorial Hospital on October 15, 1943. He stated that he was the father of two children. His past medical and surgical histories were essentially negative. The breast history began 6 months prior to admission when he noted a painless lump in the lateral middle portion of his right breast. Four months later nipple retraction was evident and 1 month prior to his application for treatment severe pain was complained of in the lumbar spine, of such severity that he could not bend nor lift heavy objects. He had received medication for this "rheumatism." There had been a loss of 8 pounds in weight during the 6 month interval.

Physical examination: The patient was well developed but slightly undernourished. The examination was without remarkable findings except for the breast condition. There was a deformity of the right breast with retraction of the nipple and dimpling of the skin lateral to the areola. There was an underlying tumor measuring 2 by 1.5 centimeters with a zone of surrounding reaction in fat. The tumor was slightly adherent to the chest wall. There were several definitely metastatic nodes in the right axilla but several smaller discrete ones could be palpated in the opposite side. The genitals were normal. Because of the roentgenographic findings the case was classified primary, inoperable.

At x-ray examination October 15, 1943, views of the chest showed no evidence of metastasis to the lungs. The film of the pelvis showed numerous small areas of increased bone density. There was suggestive evidence of the presence of several small areas of destruction in the ribs. Film of the pelvis revealed evidence of extensive metastases.

Aspiration biopsy tissue from the primary breast tumor was reported to contain "carcinoma."

At the time of admission blood was obtained for chemical analysis. The alkaline phosphatase was 7.8 units and the calcium and phosphorus levels were slightly but not significantly elevated. Castration

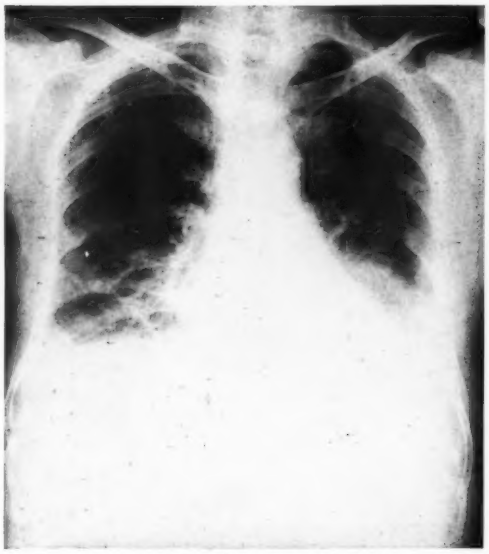

Fig. 3. Case 1. Multiple pathological fractures of the ribs of the right side.

Fig. 5. Case 1. The fractures in the ribs show definite repair with callus formation and bone replacement.

was advised and the patient acquiesced. He was admitted to the hospital for metabolic study prior to operation.

At operation December 8, 1943, a bilateral orchiectomy was done under spinal anesthesia with novocain.

Pathological examination revealed "Essentially normal testicles."

The patient remained in the hospital for 3 weeks after operation. This was essential for certain metabolic studies. His convalescence was not satisfactory for he did not show any relief from the bone pain which Patients 1 and 3 obtained. He did not put on weight. Apparently cheerful at times, he was depressed on other days. While there was a slight initial drop in the alkaline phosphatase, it never became normal.

Fig. 4. Case 1. Osteolytic metastases to the left side of the 4th lumbar vertebra. Numerous diffuse areas in the pelvis.

Fig. 6. Case 1. Repair in 4th lumbar vertebra strikingly represented; while questionable areas of bone change persist in pelvis these have not progressed since orchiectomy.

Fig. 7, left. Case 3. Definite metastasis is shown in the body of the 12th dorsal vertebra.

Fig. 8. Case 3. There is evidence of bone regeneration in the body of the 12th dorsal vertebra. Similar change is noted in the 1st lumbar. Films were made 8 months after orchiectomy.

There was no evidence of repair in the destructive areas of bone. One month after operation the phosphatase was 19.8 units and 1 month before death it had risen to 38.8 units. Death occurred April 4, 1944, 4 months following orchiectomy.

Castration in no way altered the clinical course in this 39 year old male. His pain was not relieved. The total duration of life from the onset of symptoms to death was about 12 months. The failure, in this case, to respond favorably following orchiectomy may have been due to the patient's comparatively young age.

CASE 6. A. P., was by descent a German Catholic, aged 63; married and the father of two children. His surgical and medical histories were noncontributory. In May, 1943, he noted a painless lump in his left breast and since it caused him no trouble he did not seek any relief for the condition until he was admitted for treatment on December 1, 1943.

Physical examination revealed a well developed, well nourished and apparently healthy male. Aside from the local mammary condition the positive findings were a sebaceous cyst on the right cheek and an irreducible umbilical hernia of moderate size, present for 4 years. The genitals were normal.

Examination of the left breast showed the left nipple and areola partly ulcerated and retracted. The surrounding skin was slightly bluish. Beneath this area was a partially fixed firm mass 5 by 4 centimeters in diameter (Fig. 9). In the nearby skin several ecchymotic areas were present as well as a few discrete cutaneous nodules above the tumor and near the costal margin. The left axilla contained a mass of matted metastatic nodes as large as the primary tumor.

Aspiration biopsy tissue, December, 1, 1943, report: "Carcinoma."

X-ray examination was made December 1, 1943, film of the chest revealed evidence of metastases to the lungs most marked on the right (Fig. 10). Views of the lumbar spine and pelvis showed no evidence of bone destruction.

The patient was admitted to the hospital for study after castration was advised. An investigation of certain phases of metabolism was undertaken before the operative procedure. While the blood calcium was at a high normal level the alkaline phosphatase was not appreciably increased.

At operation on January 9, 1944, bilateral orchiectomy was carried out under spinal anesthesia with novocain. The patient left the hospital on the 20th postoperative day. Convalescence was uneventful.

The pathological report was as follows: Testes show slight to moderate tubular atrophy. Spermato-

Fig. 9. Case 6. The primary lesion in the left breast has destroyed the nipple and a good portion of the areola. The diffuse nodular metastases in the skin are indicated. Swelling in the axilla is due to the metastatic axillary nodes.

genesis is present. Interstitial cells are within normal limits."

There was an initial increase in the size of the breast lesion. Now the ulceration has healed over and the mass has decreased in size (Fig. 11). The axillary nodes do not seem to be altered in size or consistence. Recently slight edema of the left arm has been noted.

Following castration x-ray studies on March 1, 1944, were reported as follows: "Film of the chest made today when compared with the previous view reveals evidence of an increase in the extent of the metastases in the lungs."

A review of these films showed an area of decalcification in the crest of the right ilium—this finding has been persistent since admission.

On April 27, 1944, the following x-ray findings were noted:

Chest—The areas of infiltration noted previously in the right lung field are less distinctly seen at this time (Fig. 12). The lower lung field shows some peribronchial fibrosis. The left lung field is unchanged except for two small areas, one in the 6th and one in the 9th interspace posteriorly, suggestive of metastatic disease. These were indistinctly seen on the previous film.

Fig. 10. Case 6. Pulmonary metastases are most marked on the right.

On May 27, 1944, stereoscopic pelvic and detailed views of the right ilium—in the region of the crest of the ilium there are irregular areas of decalcification, definitely suggestive of metastasis.

The study of the blood chemistry showed no alteration.

In this patient, as in the first patient, after four to five months, there has been an arrest in the growth of the primary lesion with some regression in the tumor, healing in the skin and disappearance of the cutaneous metastases. The axillary nodes have apparently not regressed. There has been noticeable diminution in the size and extent of the pulmonary metastases. Early metastases to the right ilium have not extended since castration. He maintains his weight and is in an excellent state of health and nutrition. Aside from slight pain in the left arm, due to edema, he is comfortable.

THE CLINICAL RESULTS OF BILATERAL ORCHIECTOMY

The following summary has been based on an analysis of the 6 patients who had bilateral orchiectomy and whose histories are analyzed in Table I.

Fig. 11. Case 6. The nipple is gradually returning to normal. The skin ulceration has healed over. The cutaneous metastases are regressing. The swelling in the axilla is unchanged. Note the loss of hair compared with Figure 9. This is the condition 5 months after orchiectomy.

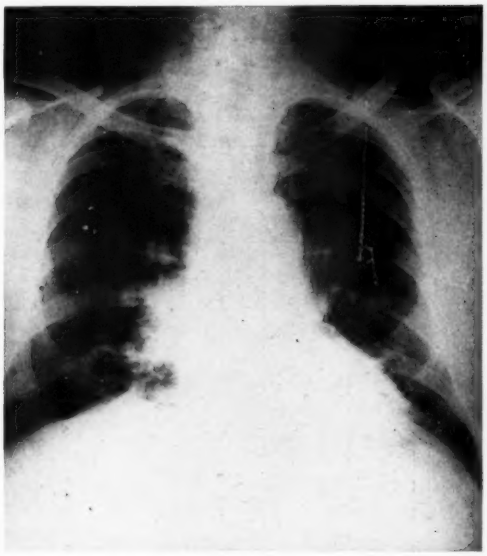

Fig. 12. Case 6. There has been decided regression in the extent and density of the pulmonary metastases.

To date no data on laboratory animals have been found which parallels the present clinical study. If it did exist we believe that such studies would be inconclusive for we may reasonably infer that there exists at present no relationship between animal research and human experiment in such a problem.

We must call attention to the relatively small number of male patients with mammary cancer available in the clinic. From this group a smaller number have been considered suitable for the type of therapy under report. And from these few an even smaller group have been obtained who would consent to undergo surgical castration.

One may reason that if the procedure is of value in inoperable cases of male breast carcinoma, it might prove a beneficial form of therapy alone, or as an adjunct measure in the treatment of operable breast cancer in the male. We cannot as yet justify it.

SUMMARY

In summarizing this group we may comment briefly on Case 2, the primary operable patient who became inoperable about 7 months after radical mastectomy. He was treated with progynon after orchiectomy was refused and osseous metastasis had appeared. He had an associated cirrhosis of the liver. When the pain from the metastatic deposits in bone became unbearable he agreed to castration. The operation was performed under local anesthesia without incident, but the patient died suddenly 3 days after orchiectomy. Obviously the effects of castration could not be studied in this case.

In Case 5, the patient, a young man of 39 years admitted to the clinic with widespread disease of the skeletal system and intense pain, submitted to bilateral orchiectomy, surviving for 4 months. In the postcastration period there was no relief of pain and no evidence of reparative change in the skeletal metastases. It may be that his comparative youth, contrasted with the four older males in this group who have had favorable clinical responses, may be the reason for the unsatisfactory re-

TABLE I.

Case	Clinical classification	Mammary history	Pathology	Physical findings on admission	Treatment	Blood chemistry						Pathological report on testes	Course
						X-ray studies	Date	Calcium	Phosphorus	Alkaline phosphatase	Date castration		
1. M.S. Age 72 White, Italian Catholic. Married. 2 children. Date of admission—4-28-41	Primary inoperable, left	Ulcer of nipple, 4 mos. Mass 5 by 6 by 2 cm. Axillary nodes	2-9-42 Formal biopsy: Infiltrating carcinoma—Grade II	Nipple and areola destroyed. Remained away 9 mo. after mastectomy was advised	None except orchiectomy	4-30-41, negative	2-5-42	10.5	3.62	5.9		Atrophy and interstitial cell hyperplasia	Remarkable clinical regression of primary lesion with bone regeneration. Return to normal of blood chemistry. Questionable relapse
						1-30-42, widespread	.....			.....	2-9-42		
						4-4-42, no change	2-17-42	10.6	4.00	7.0			
						5-28-42, rib fractures healed	5-25-42	11.0	4.20	11.1			
						6-17-42, evidence of calcification	6-22-42	10.9	4.06	7.1			
						6-22-42, 8-24-42, continued improvement	1-21-43	10.6	3.80	3.5			
						5-24-43, no change	11-12-43	10.8	3.40	2.8			
						3-17-44, no change	3-17-44	10.7	3.50	3.8			
						5-25-44, ? reactivation	5-18-44	11.5	3.54	5.5			
2. J.S. Age 75 White, English Protestant. Married. 6 children. Date of admission 6-10-41	Recurrent inoperable, right	Lump 1 yr. Mass 6 by 4 cm. Axillary nodes	7-1-43 Infiltrating carcinoma Grade III. Multiple node metastases	Ulcerating lesion with involved nodes	Radical mastectomy 7-1-41. Progynon 228,000 R.U. 7-23 8-18-42: orchiectomy	6-13-41, negative						Slightly atrophic testes	Had cirrhosis of liver. Operative death 1-30-43. Estrogens reactivated?
						2-26-42, skull	2-26-42	11.2	2.39	5.4			
						3-27-42, rib, spine, pelvis	6-18-42	10.9	3.89	7.6			
						6-20-42, widespread							
						7-17-42, increased	7-17-42	11.4	4.58	9.9			
						8-7-42, increased	7-28-42	11.6	4.62	8.6			
						12-28-42, increased right lung	8-17-42 1-18-43	14.4 11.8	3.80 4.40	10.9 11.6	1-27-43		
3. B.D. Age 65 White, Austrian Jew. Married. 1 child. Date of admission 4-13-42	Prophylactic, right	Local excision 15 years before axillary dissection, 2-23-42	2-23-42 Infiltrating duct carcinoma, Grade II	Granulating scar—radical axillary dissection. No recurrence	Excision and axillary dissection elsewhere. Postoperative radiation and orchiectomy	5-27-42, ? 12 D., 1-3-4 L.	6-1-42 8-10-42	10.3 10.2	2.92 3.10	4.2 4.8		Mild atrophy	Gain in weight of 40 pounds. No pain. No evidence. X-rays show bone regeneration
						8-24-42, positive 12 D; 1-2-3 L.	4-8-43	11.4	4.18	4.7			
							4-30-43	10.3	3.56	6.6	5-8-43		
							7-12-43	10.8	3.10	3.7			
							2-7-44	11.8	3.39	2.6			
4. A.I. Age 64 White, Irish Catholic. Married. 1 child. Date of admission 6-1-43	Primary operable, left	Lump in breast, 3 weeks. Hydrocele 3 years (bilateral)	6-12-43 Local excision: Adenocarcinoma	Lump in left breast 2 cm. No nodes	None except local excision. Axillary dissection. Orchiectomy	Chest negative. No symptoms of bone metastasis	N	O N E		.....	6-12-43	Normal testes	Axilla not dissected until 10 months after excision. No metastasis

TABLE I.—Continued

TABLE I.—Continued

Case	Clinical classification	Mammary history	Pathology	Physical findings on admission	Treatment	X-ray studies	Blood chemistry: Date	Calcium	Phosphorus	Alkaline phosphatase	Date castration	Pathological report on testes	Course
5. E.S. Age 39 White, Irish Catholic. Married. 2 children. Date of admission 10-15-43	Primary inoperable, right	Lump 2 by 1½ right breast, 6 months. Loss of 8 lbs. Bilateral axillary nodes	10-18-43 Aspiration biopsy: carcinoma	Lesion with skin attachment. Several nodes. Back pain	None except orchiectomy	10-15-43, ribs	10-18-43	12.6	3.72	7.8		Essentially normal testes	Died April 4, 1944 of disease
						11-22-43, skull and pelvis	11-22-43	11.4	5.24	8.1			
							12-9-43	15.2	5.12	13.7	12-8-43		
						12-30-43, widespread	12-13-43	13.6	5.07	11.5			
						2-21-44, increase	12-20-43	13.0	3.07	9.4			
						3-20-44, increase	12-30-43	11.2	5.12	22.2			
							2-21-44	11.8	5.54	19.8			
							3-20-44	12.0	4.36	38.8			
6. A.P. Age 63 White, German Catholic. Married. 2 children. Date of admission 2-1-43	Primary inoperable, left	Lump left breast 7 mo. duration, 5 by 4 cm. Slight nipple ulceration. Cutaneous nodules. Axillary mass 5 by 4 cm.	12-1-43 Aspiration biopsy: carcinoma	5 by 4 primary 5 by 4 axillary mass. Cutaneous nodules	None except orchiectomy	10-1-43, pulmonary more marked on right	12-1-43	12.5	2.90	3.4		Slightly tubular atrophy. Spermatogenesis present. Interstitial cells normal	Breast tumor slightly smaller. Nodes unchanged. Pulmonary disease less. Pelvic metastases present on admission have not increased
							12-27-43	11.2	3.40	—			
							1-7-44	11.1	3.58	—	1-19-44		
						3-1-44, increase	3-23-44	12.1	3.60	2.3			
						3-31-44, decrease ?	4-27-44	—	4.18	2.3			
						5-24-44, pelvis positive. Lung less marked	5-5-44	12.2	3.52	4.0			

sult. Cancer of the breast in the young, female or male, is always a formidable therapeutic problem. It may likewise be significant that his alkaline phosphatase was the highest preoperative value of any of the patients in this group—8.1 units. He also had the highest initial postoperative value of alkaline phosphatase—13.7 units. At no time did this reading approach the normal value and the last phosphatase determination showed a reading of 38.8 units. The procedure in this instance must be considered a clinical failure. Of the group of 6 castrates, he is the outstanding failure.

In Case 1, a 72 year old male with widespread metastases to bone, was castrated on February 9, 1942. He had prompt relief from pain and has been comfortable since that time. Skeletal metastases have shown marked reparative change; all the pathological fractures in bone having healed with a firm callus which subsequently ossified. His general condition is good; he is in an excellent state of nutrition; the blood chemistry has returned to normal. One of the most striking results in this case has been the continued regression in the primary cancer of the left breast. The ulcerating tumor has now been completely replaced by a cicatrix. However, at the present time there is some question of reactivation especially in the skull. Twenty-eight months have elapsed since castration.

In Case 3, the patient submitted to castration on May 8, 1943, and was relieved promptly of the pain caused by metastases to the lower dorsal and lumbar vertebrae. While his blood chemistry never showed an abnormally high rise, his preoperative alkaline phosphatase of 6.6 units now is 2.6 units. X-ray films show evidence of bone regeneration. There has been a gain in weight. No evidence of local recurrence is noted nor are there new areas of metastasis and the pain has been completely relieved—a very gratifying clinical result 13 months after bilateral orchiectomy.

The third case with a favorable result has now gone 1 year after castration. He was the only primary operable patient in the group and his breast cancer was treated only by local excision and bilateral orchiectomy.

TABLE II.—METABOLIC EFFECTS OF ORCHIECTOMY

Patient	Disorder	Period, days	Plasma volume Ml	E.C.W. Lit	Serum concentration, MEq/L of					
					Na	K	Ca	HCO_3	CL	PO_4
J. S.	Carcinoma prostate	Control, 15	3050	14.1	145	5.2	5.9	28.2	97.5	3.8
		Postoperative, 15	2980	14.3	148	5.1	6.2	29.0	100	4.0
E. S.	Carcinoma breast	Control, 12	1940	12.0	142	5.5	6.0	27.2	88	4.0
		Postoperative, 12	2100	10.5	140	5.0	6.6	25.0	94	4.6
A. P.	Carcinoma breast	Control, 18	3390	18.75	146	5.1	5.6	26.5	101	3.5
		Postoperative, 18	3500	18.3	140	4.8	5.0	28.0	97	4.0
G. F.	Carcinoma prostate	Postoperative, 45	3050	11.5	144	5.1	5.6	29.0	100	3.7
I. L.	Carcinoma prostate	Postoperative, 40	2600	12.2	144	4.9	5.7	28.6	97	3.9

ML=milliliters.
E.C.W.Lit.=Liters of extracellular water.
MEq./L=milliequivalents/liter.

This unusual approach to the control of mammary carcinoma in the male has resulted in the following observations: (1) A radical axillary dissection 10 months after local excision and castration revealed no evidence of metastasis to the axillary nodes. (2) There has been no recurrence at the site of the local excision and the patient has not developed distant metastatic areas to date. However, one cannot be certain that local excision alone might have controlled the tumor process.

In Case 6 patient was castrated in January 1944, following the discovery of definite pulmonary metastasis on his initial visit to the clinic. Five months after operation there has been a noticeable decrease in the extent and character of the pulmonary metastases. A single area of bone destruction in the crest of the right ilium has shown no further progression. The primary tumor in the breast has shown moderate healing and regression, but the axillary metastases have as yet shown no signs of alteration. There have been no significant changes in the blood chemistry. The patient has maintained his weight and is in good general condition.

TABLE III.—METABOLIC EFFECTS OF ORCHIECTOMY

Patient	Disorder	Period, days	Average nitrogen balance gm. per day	Average creatine output gm. per day	Total circulating protein gm.
J. S.	Carcinoma prostate	Control, 15	+6.1	0.4	212
		Postoperative, 15	+6.0	0.4	197
E. S.	Carcinoma breast	Control, 12	−0.2	0.05	144
		Postoperative, 12	+0.2	0.08	147
A. P.	Carcinoma breast	Control, 18	+4.8	0.12	235
		Postoperative, 18	+5.2	0.09	247
G. F.	Carcinoma prostate	Postoperative, 45		0.2	
I. L.	Carcinoma prostate	Postoperative, 40		0.14	

METABOLIC EFFECTS OF ORCHIECTOMY

It is now a common observation that after orchiectomy, patients with carcinoma of the prostate which has metastasized to bone often show considerable clinical improvement. This benefit, as a rule, consists of a marked decrease of pain at the sites of skeletal metastases, increased appetite, gain in weight and muscular tone. Improvement of this nature, likewise, was noted to occur after operation in 4 of the 6 patients with breast cancer included in the present study.

The symptomatic change after orchiectomy most likely is related to the hormone imbalance effected by the surgical procedure. The nature of this imbalance is not, of course, clear, but it is reasonable to believe that metabolic changes are affected by a decreased androgen formation or overactivity of naturally occurring estrogens. The latter assumption appears all the more likely since the administration of estrogens to patients with prostatic cancer metastatic to bone in many instances is attended by equal or better success than that induced by orchiectomy (7). Since the administration of certain estrogens

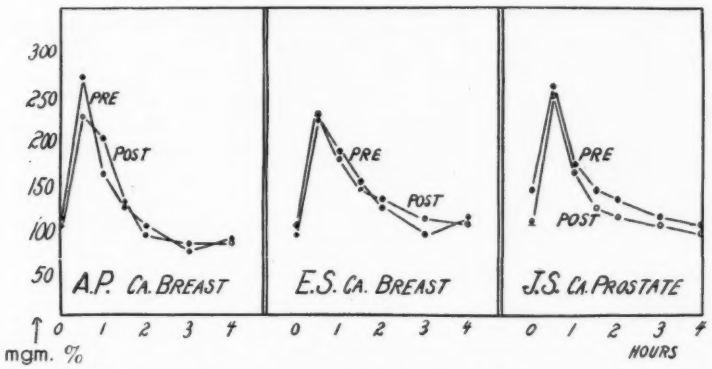

Fig. 13. Intravenous glucose tolerance curves before and after orchiectomy show no change in the carbohydrate utilization. A. P., Case 6; E. S., Case 4; J. S., prostatic cancer whose glucose tolerance was likewise unchanged after orchiectomy. Intravenous glucose, 0.5 gram per kilogram.

and other related steroids apparently can induce characteristic metabolic changes, these alterations were sought for after orchiectomy in 2 of the 6 men with breast cancer and in an additional 3 patients with carcinoma of the prostate.

In particular, measurements were made of the effects of the surgical procedure on:

A. Fluid and electrolyte balance. Previous studies from this hospital have demonstrated that the administration of α-estradiol benzoate to women before and after the menopause and to men with prostatic cancer induces a significant rise in both extracellular water and plasma volume (2). It is interesting to note that a similar change results from the administration of large amounts of testosterone and testosterone propionate (3). However, from 12 to 18 days after orchiectomy no significant change had occurred in the volume of extracellular water or plasma in 2 patients with cancer of the breast and 1 patient with carcinoma of the prostate. Likewise, in the 2 remaining patients with prostatic carcinoma in whom these measurements were made only 3 months after operation, the values obtained were within normal limits (Table II). Furthermore, orchiectomy apparently had no persistent effect on the concentrations of sodium, potassium, calcium, bicarbonate, phosphate, or chloride in the serum of the patients studied.

B. Nitrogen balance and protein fabrication. The now well known effect of certain androgens (principally testosterone and testosterone propionate) to induce nitrogen retention (6) suggested that a temporary negative nitrogen balance might obtain in males subjected to castration. In a group of 3 individuals studied here (2 with carcinoma of the breast and 1 with carcinoma of the prostate), nitrogen balance studies were made for from 12 to 18 days before and for a like period after operation. No change in nitrogen balance was found to have occurred in this time. The total circulating protein of these individuals, likewise, remained unaltered (Table III).

C. The urinary excretion of creatine. Since testosterone and methyl testosterone especially appear to exert a considerable influence on the urinary excretion of creatine (4) there was reason to believe that this function might be effected by the castration. This was not found to be the case in the 2 patients with breast cancer and the 1 patient with carcinoma of the prostate. Likewise, the 2 other individuals with prostatic tumor excreted only normal amounts of creatine (Table III).

D. The utilization of carbohydrate. There is no satisfactory evidence that hormones particularly potent as androgens or estrogens exert an influence on carbohydrate metabolism as do corticostrone or certain other steroids of adrenal cortical origin. Nevertheless, it ap-

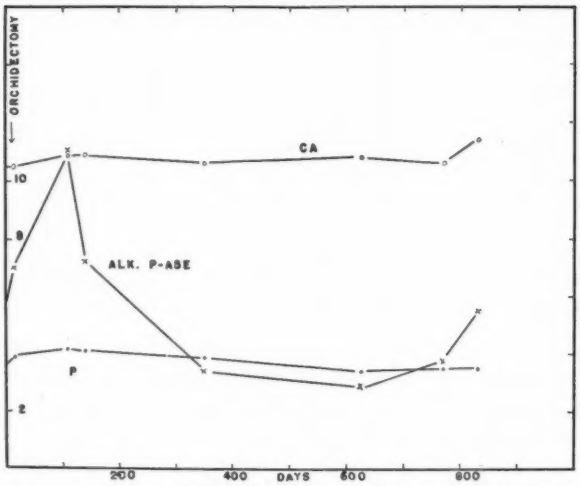

Fig. 14. Case 1. The serum alkaline phosphatase rose following orchiectomy, then fell to normal, and remained in the normal range until there was clinical evidence of relapse. Serum calcium and phosphorus were normal throughout. Serum alkaline phosphatase in Bodansky units per 100 c.c. Serum inorganic phosphorus in mgm. per 100 c.c. Serum calcium in mgm. per 100 c.c. Urine calcium in mgm. excreted per 24 hours.

peared to be of interest to ascertain whether or not the hormone imbalance conceived to occur after orchiectomy might be reflected in an unusual carbohydrate utilization.

Accordingly, 2 patients with carcinoma of the breast and 1 patient with carcinoma of the prostate were maintained on consistent diets as described by Thorne (14). When these subjects were in nitrogen balance, an estimation of their carbohydrate metabolism was obtained from their intravenous glucose tolerance curves both before and after orchiectomy. These measurements, made by the technique described by Thorne and associates (14), failed to indicate any change in carbohydrate utilization (Fig. 13) after operation.

SUMMARY

It would appear, therefore, that of the metabolic phases measured, none changed significantly in the 12 to 18 days after orchiectomy in the patients studied. Changes known to be induced by testosterone or α-estradiol apparently do not occur simultaneously with clinical symptomatic improvement in patients subjected to orchiectomy.

BIOCHEMICAL EFFECTS OF ORCHIECTOMY

Before the blood chemical findings on the present cases are discussed it will be well to review the general significance of chemical changes in patients with cancer metastatic to bone. Alkaline phosphatase is produced in large amounts in bones which are attempting to repair damage. When cancer of soft part origin metastasizes to bone, the bone may or may not respond to the injury with the production of new osseous tissue. When an attempt at repair is made the alkaline phosphatase of the serum rises and the metastases are osteoplastic. When, as in the majority of bone metastases from carcinoma of the breast, no attempt at repair is made, the alkaline phosphatase of the serum remains normal, and the lesions are osteolytic. If the process of bone destruction is very rapid, the calcium and phosphorus of the serum may rise to high, or even dangerous, levels. Thus the alkaline phosphatase of the blood may be taken as an index of the rapidity of bone formation, and the calcium and phosphorus of the blood as an index of the rapidity of bone destruction.

We have shown elsewhere (10) that treatment with either testosterone propionate or with estrone caused an increase in the serum calcium of female patients with carcinoma of the breast metastatic to bone. The increase was apparently due to increased osteolysis caused by rapid growth of the tumor in the bone. It did not occur in patients with breast cancer who were without bone metastases.

Several investigators (7, 11, 13) have found that, when patients with carcinoma of the prostate metastatic to bone are orchiectomized, the serum alkaline phosphatase, which is usually elevated before treatment, rises still higher. In our series, this rise occurred in two-thirds of the cases. A similar rise was observed in patients treated with stilbestrol, but only in about one-fourth of the cases. The increase was temporary, persisting for only 2 or 3 months, and was followed by a drop to or below the initial level. The increase in the serum alkaline phosphatase was usually associated with an increase in the degree of osteoplasia of the bone lesions, but in some patients this appeared to indicate healing, while in others the metastatic lesions became larger and more numerous.

It seems probable that the regenerative capacity of the injured bone is stimulated by some one of the many endocrine changes associated with castration. The effect is not confined to the male sex, since we have also seen it in female patients with carcinoma of the breast who have undergone either surgical or roentgen castration. The mechanism of this stimulation remains obscure.

Of the patients forming the subject of the present report, Case 1 showed changes in serum alkaline phosphatase very similar to those commonly seen in castrated patients with carcinoma of the prostate metastatic to bone. The alkaline phosphatase was slightly elevated at 5.9 units per 100 cubic centimeters before castration, began to rise immediately after operation, and reached 11.0 units in 3½ months. It then dropped, reaching normal in 1 year and remaining within normal limits for another year. There was no striking increase in the degree of osteoplasia of the bone lesions, but the process was arrested and some healing took place. The serum calcium and phosphorus were within normal limits throughout, indicating that the rate of bone destruction was never very rapid. At present, 28 months after castration, the serum alkaline phosphatase has risen slightly, and there are x-ray indications of possible relapse. The chemical changes are shown graphically in Figure 14.

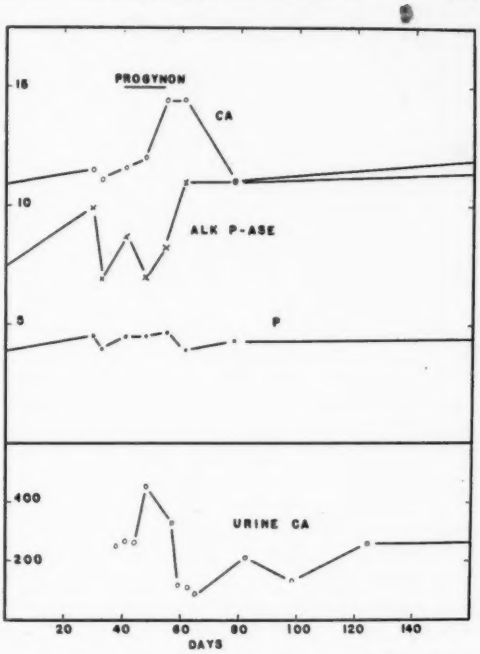

Fig. 15. Case 2. The serum calcium and the urinary excretion of calcium rose during progynon treatment and then fell to their former levels. Changes in serum alkaline phosphatase were difficult to interpret owing to concurrent cirrhosis of the liver. Serum alkaline phosphatase in Bodansky units per 100 c.c. Serum inorganic phosphorus in mgm. per 100 c.c. Serum calcium in mgm. per 100 c.c. Urine calcium in mgm. excreted per 24 hours.

In Case 2 there was considerable elevation of the serum alkaline phosphatase throughout the period of observation. The patient probably had cirrhosis of the liver, and, in liver disease, alkaline phosphatase may be retained in the blood, instead of being excreted in the bile, as it normally is. Hence, in this case, the level of serum alkaline phosphatase cannot be taken as an index of bone activity. The serum calcium, however, showed a highly significant rise during α-estradiol therapy. Before treatment the serum calcium was normal, varying

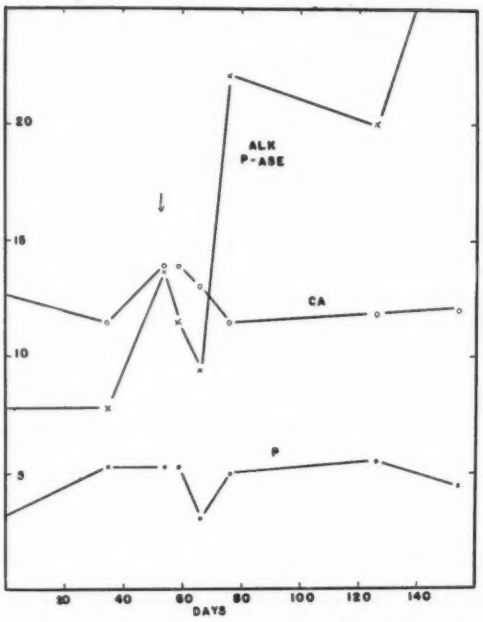

Fig. 16. Case 5. Serum alkaline phosphatase, phosphorus, and calcium were all elevated before orchiectomy, and showed only transitory improvement following operation (indicated by arrow). Serum alkaline phosphatase in Bodansky units per 100 c.c. Serum inorganic phosphorus in mgm. per 100 c.c. Serum calcium in mgm. per 100 c.c. Urine calcium in mgm. excreted per 24 hours.

between 10.9 and 11.4 milligrams per 100 cubic centimeters on three determinations. It began to rise immediately on the beginning of treatment, and reached 14.4 milligrams per 100 cubic centimeters in 2 weeks. Treatment was then discontinued, and the calcium fell slowly to 11.0 milligrams. The rise in serum calcium was probably due to increased osteolysis caused by the acceleration of the growth of the metastatic tumor under the influence of α-estradiol. The chemical changes are shown in Figure 15.

In Case 3 patient showed occasional slight elevations in serum alkaline phosphatase and serum calcium, but the changes were too small to be significant.

In Case 5 patient showed, prior to castration, elevations in serum alkaline phosphatase (7.4 to 13.6 units per 100 c.c.), in serum phosphorus (3.2 to 5.1 mgm. per 100 c.c.), and in urinary excretion of calcium (420 to 580 mgm. every 24 hours). This appeared to indicate that osteolysis was rapid, as was also shown roentgenographically, but that some attempt at bone repair was being made. Immediately after castration there was a shift toward normal in all chemical findings, but this change lasted for only 2 weeks, after which there was a reversion to, or above, the former high levels. Simultaneously there was a deterioration in the clinical condition of the patient. It is not clear whether the rise in alkaline phosphatase was a response to castration or to the increased activity of the metastatic deposits in the bones. The chemical changes are shown in Figure 16.

In Case 6 patient developed bone metastases late in the period of observation. His blood chemistry was normal except for a persistent borderline elevation in serum calcium. The elevation was too small to be considered definitely pathological.

Determinations of serum acid phosphatase were made at intervals on these patients, and no abnormalities were found. This was to be expected, since, as far as is known at present, serum acid phosphatase is never increased except in the presence of metastasizing carcinoma of the prostate.

CONCLUSION

We may summarize the clinical results of this study by stating that bilateral orchiectomy may have been responsible for the temporary regression of the primary lesion in 2 instances, quite striking in 1 of the cases. It has possibly prevented recurrence in the primary operable patient treated only by local excision, and may have prevented local recurrence in 1 other instance. The procedure has caused regression and repair in the secondary deposits in bone as well as in lung. The clinical regressions in this study compared with those reported for inoperable and metastatic carcinoma of the prostate have had in some cases the same dramatic cessation of pain caused by bone involvement. The clinical improvement has been as satisfactory and as long. In fact, we think this procedure for male breast cancer may parallel the striking results of orchiectomy for the advanced cases of prostatic cancer. One in-

operable case has now survived 28 months after castration, and one 13 months. Both are in excellent states of nutrition and are free from pain. Two have lived for nearly 6 months with regression of their disease and give clinical promise of surviving for equally long periods. Two of the patients have shown definite reparative changes in metastatic deposits in bone, while one with a solitary area of bone involvement has shown no evidence of progression of the disease, nor have other areas developed since castration. This latter patient has had regression in the extent of his pulmonary metastases. In two instances the primary lesions have become smaller. The case of longest survival shows only a cicatrix, and the other, regression in the ulceration and in the cutaneous nodules. The latter patient has not survived a long enough time to evaluate properly the effect of orchiectomy on the breast tumor.

In the histological examination of the testes of the 6 orchiectomized patients, essentially normal gonads were found. The mammary cancer had not metastasized to the testicles. This is in striking contrast to the findings in 33 women who were castrated for therapeutic control of breast cancer. In this group 9 patients had mammary carcinoma metastatic to the ovaries.

The studies on two of the orchiectomized patients led to a conclusion that of the metabolic phases measured—(1) fluid and electrolyte balance; (2) nitrogen balance and serum protein fabrication; (3) urinary excretion of creatine; and (4) the utilization of carbohydrate—none changed in 12 to 18 days after operation. This failure to demonstrate changes known to be induced by the administration of testosterone or α-estradiol, shows that these changes are not necessary to produce clinical symptomatic improvement.

In one castrated patient the same changes in the serum alkaline phosphatase were seen which were observed regularly in patients with carcinoma of the prostate metastatic to bone following orchiectomy. In two castrated patients there were no conspicuous changes in the calcium, phosphorus, or alkaline phosphatase of the serum, and in one the findings indicated continuing progress of the disease. In the patient treated with α-estradiol there was a rise in serum calcium similar to that found in female patients with bone metastases from carcinoma of the breast who have received estrogens. Thus, in this small series of patients, there is a marked lack of uniformity in the response to endocrine treatment of the blood changes caused by bone metastases. Further observation will be necessary before the cause of this variability can be determined.

We must again call attention to the small number of cases under report. The value of the procedure will only be determined by observations on a larger group.

REFERENCES

1. ABELS, J. C. Personal observation.
2. ABELS, J. C., YOUNG, N. F., and TAYLOR, H. C., JR. Metabolic effects of α estradiol. In preparation.
3. Idem. The effects of testosterone and testosterone propionate on the fabrication of plasma protein. J. Clin. Endocr., in press.
4. BUHLER, F. Zschr. ges. exp. Med., 1933, 86: 638.
5. Idem. Quoted by Sutton, M. B.
6. Conference on Bone and Wound Healing. Second Meeting, pp. 61–70, 1942.
7. DEAN, A. L., WOODARD, H. Q., and TWOMBLY, G. H. J. Urol., Balt., 1943, 49: 108–117.
8. DOBRINER, K. Personal communication.
9. FARROW, J. H., and ADAIR, F. E. Science, 1942, 95: 654.
10. FARROW, J. H., and WOODARD, H. Q. J. Am. M. Ass., 1942, 118: 338–343.
11. HUGGINS, C., and HODGES, C. V. Cancer Research, 1941, 1: 293–297.
12. SUTTON, M. B. J. Clin. Endocr., 1941, 1: 882.
13. SULLIVAN, T. J., GUTMAN, E. B., and GUTMAN, A. B. J. Urol., Balt., 1942, 48: 426–458.
14. THORNE, G. W., KOEPF, G. F., and LEWIS, R. H. J. Clin. Invest., 1940, 14: 772.

CHOICE OF INCISION IN GALL-BLADDER SURGERY AS A FACTOR IN PREVENTING WOUND DISRUPTION, EVISCERATION, AND HERNIATION

JOSEPH L. DeCOURCY, M.D., F.A.C.S., Cincinnati, Ohio

CONSTANTLY improving surgical technique has eliminated the hazards and many of the aftermath complications of surgical procedures. Thus, in addition to lowered mortality rate, the period of recuperation has been markedly reduced and prognosis improved.

In spite of advances in technique, the surgeon is still frequently faced with the postoperative catastrophe of wound disruption, evisceration, and herniation. This fact is especially true in regard to abdominal operations involving the right upper quadrant.

The comprehensive report in 1932 of Sokolov of Leningrad, analyzing 730 cases of wound disruption with evisceration, aroused extreme interest here and abroad as to the causes and prevention of this unfortunate complication. His analysis based on over 1,000 questionnaires sent out to surgeons throughout Europe showed an incidence of dehiscence in 2 to 3 per cent of all abdominal operations.

Bowen, in a review of the American literature up to 1940, found the incidence from 0.24 per cent in White's series of 19,473 laparotomies to 3.05 per cent in Hinton's series of 621. The mortality rate ranged as high as 75 per cent, although the general average was from 25 to 40 per cent in the various series of cases.

The factors which contribute to wound disruption may be inherent either in the patient or in the technique employed at operation. I am inclined to think that the surgeon can assume responsibility for both eventualities. Certainly, in view of the high mortality rate alone, he is honor-bound to study the possible cause and prevent their occurrence in so far as he is able.

From the reported literature, it may be discerned that neither sex nor age plays a distinct rôle. Rupture may occur at any time during the postoperative course; but it is more usual during the first 2 weeks, more specifically on the eighth or ninth day. Metabolic disturbances such as diabetes, tuberculosis, and nutritional anemia, also general physical debility, emaciation and old age may be considered predisposing causes. This is especially true of malignant lesions, which comprise approximately 25 per cent of disruptions. The farsighted surgeon will by careful treatment before operation prepare such patients so that they are in the best possible physical condition before surgery is employed.

Infection and drainage, which at one time were considered primary causes of wound disruption, have been relegated to a minor position in view of the fact that by far the larger percentage of such cases recover without complications and those that do disrupt represent a small percentage of the total.

Considerable attention has been focused on suture materials as a factor influencing wound disruption. Although there has been heated controversy concerning the undesirability of catgut for suturing because of rapid absorbability and loss of tensile strength, it still has advantages over other materials—still is preferred by most surgeons. Theoretically, there is much room for argument about this point. The fact remains, however, that disruptions occur regardless of the suture material used.

The digestion of sutures and softening and edema of the tissues accompanying disruption have been attributed by some to escape of pancreatic secretions.

The rôle of sensitivity has been considered as a contributory factor to wound disruptions. Experimental work (2) has shown that sensitivity to catgut can be produced in guinea pigs with resulting gaping of the wound. Clinically such sensitivity has been demonstrated by skin tests. These findings may pertain to a

From the Department of Surgery, DeCourcy Clinic.

few selected cases, but they certainly are not related to the large number of disruptions reported. There has been no substantiation of the allergy factor.

There is no doubt that intra-abdominal pressure, such as coughing, sneezing, vomiting, and distention, contributes to the occurrence of evisceration and herniation. It must be realized, however, that there are many cases in which increased intra-abdominal pressure produces no such untoward effects. It is only when tissue impairment already exists that pressure exerts any influence. It must, therefore, be considered a secondary rather than a primary factor. Proper postoperative care can to a large extent eliminate these complications.

It is my opinion that the primary factor in wound disruption with subsequent evisceration and herniation lies in the incision: first, in the choice of the incision for the individual patient, then in gentleness in handling the tissues, and, last, adequate closure of the wound.

The greater incidence of upper abdominal disruption is probably due to the fact that the abdominal fascia is so distributed that the lower layers of the abdomen are stronger. Next to malignant lesions, surgery on the biliary tract has accounted for the major number of wound disruptions reported. It is in these operations on the gall bladder that we, at the DeCourcy Clinic, have succeeded in the prevention of dehiscence by the individualization of the incision plus the maintenance of good surgical technique. With this procedure we have experienced no wound disruptions in a large series of cases within the past 2 years.

I deem it advisable here to review the principles of wound healing of which every surgeon should be cognizant. The foremost aim in the development of tensile strength of the wound is regeneration of fibrous tissue or fibroplasia, as this is commonly called. Then there is proliferation of epithelial and connective tissue cells bordering the incision, followed by regeneration of capillaries which penetrate the exudate. This reparative tissue is termed granulation tissue. In the next process the young connective tissue undergoes shrinkage, the cells become spindle-shaped, the newly formed intercellular collagen fibers contract and squeeze the capillary loops into atrophy.

The essential requirements for an incision for operation on the gall bladder and bile ducts are ease of execution and rapidity of closure. It should afford adequate exposure for visibility and manipulation of abdominal organs, permitting enlargement if necessary.

Certain anatomic principles should not be overlooked. The incision should traverse muscle rather than fascia, as the scar left in the peritoneum is best protected by muscle. The muscles should be split in the direction of their fibers rather than cut through. The rectus muscles, however, may be cut transversely without seriously weakening the abdominal wall, as such a cut passes between two adjacent nerves without injuring them. No nerves should be divided.

In referring to the literature, we find a formidable array of types of incisions for gall-bladder surgery both anatomic and nonanatomic. I do not here intend to discuss them all but shall concentrate only on those we popularly employ, namely: (1) hockey stick (Mayo-Robson), (2) right rectus (Kammerer), (3) midline (Kammerer), (4) right rectus (high Deaver), and (5) transverse incision.

The hockey stick or Mayo-Robson incision is made through the right rectus near its outer border in a line parallel with its fibers. The incision starts at the costal margin and extends vertically downward for from 5 to 8 centimeters. The upper end is carried obliquely as high as possible in the interval between the ensiform cartilage and the right costal margin. The posterior sheath of the rectus and peritoneum are divided together.

The right rectus incision of Kammerer starts at the level of the umbilicus, half an inch medial from the lateral border of the right rectus muscle. It runs upward along the lateral border of this muscle to the costal margin. The skin, superficial and deep fascia and the anterior sheath of the rectus muscle are cut longitudinally. The incision of the deep fascia is made approximately three-quarters of an inch closer to the midline. The rectus muscle is retracted inward from the outer edge of rectus or outward from the midline. The posterior sheath and peritoneum are cut longitudinally. The value of this incision depends on the fact that the rectus is not cut and that this muscle

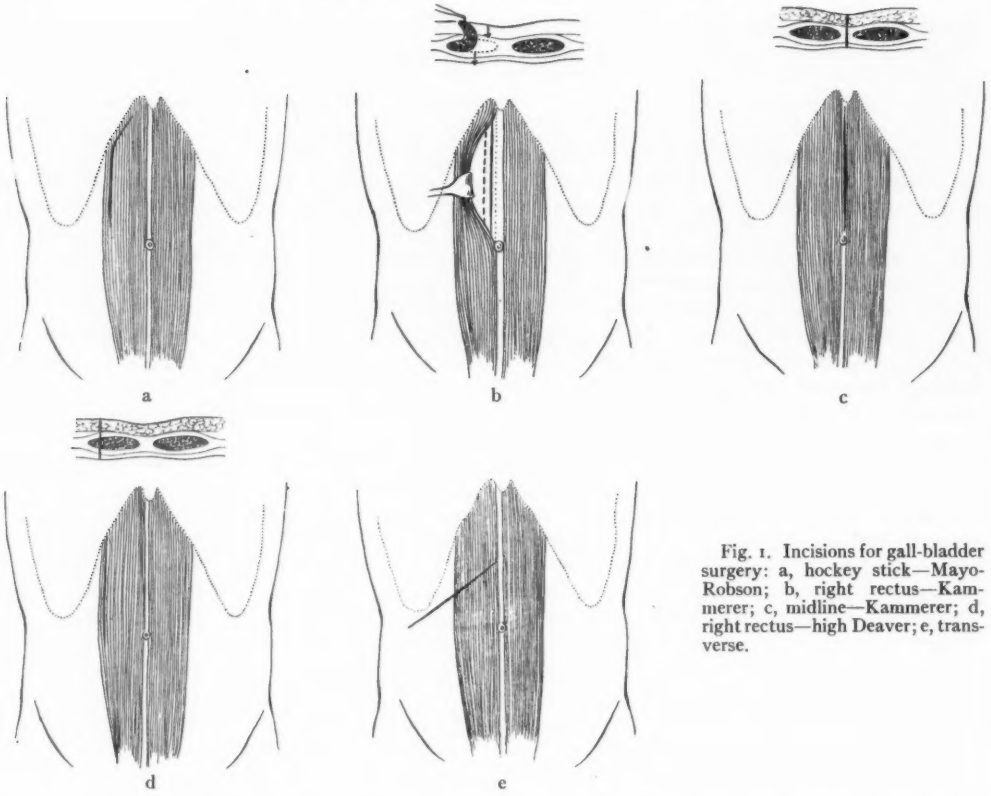

Fig. 1. Incisions for gall-bladder surgery: a, hockey stick—Mayo-Robson; b, right rectus—Kammerer; c, midline—Kammerer; d, right rectus—high Deaver; e, transverse.

protects the incisions in the peritoneum and fasciae after the wound is closed.

The midline incision, which has been in use for the longest period of time, presents the advantages of rapid opening and closure and gives a good view of the entire abdomen. For this reason it is an excellent incision for exploratory purposes. The objectionable feature of the incision is that it cuts the linea alba; i.e., the terminal fibers of the aponeurosis of all lateral muscles perpendicular to their course. To avoid the ligamentum teres, the incision at the level of the umbilicus flanks slightly to the left of the midline on to the muscle, but ends at a point parallel to the umbilicus.

The right rectus incision of Deaver starts at the level of the costal margin one-fourth to one-half inch medial from the outer border of the right rectus muscle. It runs downward to approximately 1 inch below the umbilicus. The skin, fascia and the muscle fibers are split longitudinally.

The transverse incision starts about 1 inch to the right of the midline and directly outward about 2 inches below the costal margin parallel to the "fissures of Langer." The external fascia of the rectus muscle is cut across in the same direction, while the fascia of the external oblique muscle is split in the line of the fascial fibers. With the fingers inserted between the exposed rectus muscle and the posterior sheath of the rectus, two arteries usually found in the rectus muscle can often be palpated and ligated before the muscle is incised. The rectus muscle is then split across its entire breadth. The deep oblique muscle and the transversalis muscle are split in the direction of their fibers. The peritoneal cavity is opened transversely.

With the years the trend of many surgeons

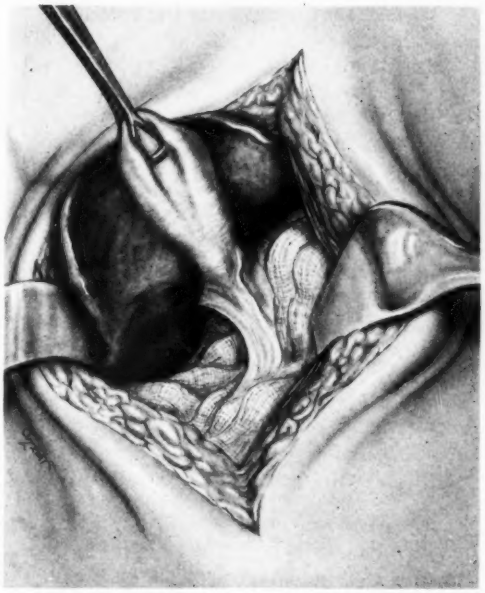

Fig. 2. Exposure of gall bladder through vertical incision showing folding of liver on elevation.

has become more and more away from vertical incisions in gall-bladder surgery. Some have even adopted the transverse incision exclusively. This appears to me to be an extreme measure, as the vertical incision presents certain advantages over the transverse incision. I wholly disagree with surgeons who suggest that the transverse incision be used in all operations on the gall bladder. At the DeCourcy Clinic, we have employed this incision satisfactorily in approximately 50 per cent of cases.

Our choice of incision depends upon the physical structure of the individual. For the asthenic type of individual, i.e., the thin, long chested person, we have found that the necessary higher exposure can best be obtained with the vertical incision.

The transverse is our incision of choice in the obese individual. This not only gives excellent exposure but also carries less trauma, causes less embarrassment to respiration and allows the liver to be elevated without folding on itself. This latter point is doubtlessly a great advantage in dealing with the obese patient, as we have often experienced such difficulty when we have had to contend with a thick abdominal wall.

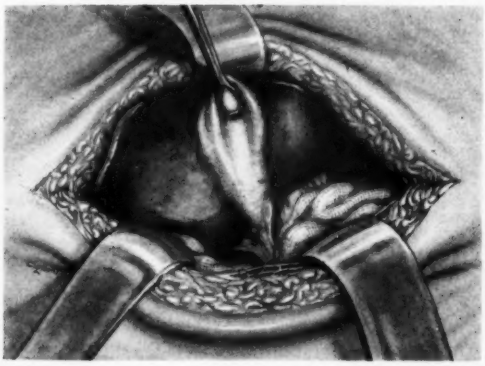

Fig. 3. Exposure of gall bladder through transverse incision.

Because of the limited exposure provided by such an incision, it does not allow for exploration; as when employing the McBurney incision for appendicitis, the diagnosis must be certain before the operation is performed.

The vertical incision, on the other hand, gives excellent exposure and is ideal for exploratory purposes. The main objection is the difficulty of closure, which we seem to have been able to surmount. It is well known that the midline incision traverses the linea alba, which is poor in its blood supply. For this rea-

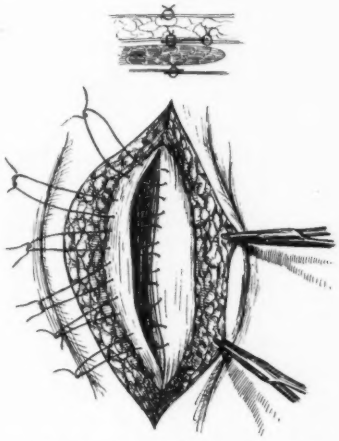

Fig. 4. Overlapping of fascial layers (Blake) when vertical incisions are used.

son a sudden or unusual contraction of the transverse or oblique muscles of the abdomen, especially when intra-abdominal pressure is exerted, would tend to pull it apart. The value of the right rectus incisions lies in the fact that the muscle protects the incisions in the peritoneum and fasciae after the wound is closed, and there is little damage to the nerve supply.

We have entirely eliminated the difficulty involved in closure of vertical incisions by employing a "Blake" closure of the fascia, just as performed in a secondary operation for incisional hernia. It is surprising with what ease this can be done at the primary operation. When the abdomen is entered, the fascia is stripped on both sides and overlaid as sutured. Drainage when necessary is brought out through a separate stab wound. The actual extra time consumed in the stripping and closure without undue haste amounts to 10 minutes.

All incisions are closed by careful approximation of anatomic structures. Tension is avoided, and gentleness in the handling of tissues is stressed.

The fact that, employing the technique described, we have been able to prevent wound disruption, evisceration, and herniation after surgery on the biliary tract has prompted me to report these findings, especially since many surgeons are leaning to the indiscriminate use of the transverse incision in all cases.

CONCLUSIONS

It is within the surgeon's power to prevent the occurrence of wound disruption, evisceration, and herniation which frequently occur in operations involving the right upper quadrant.

By individualizing the type of incision used, by careful handling of the tissues and by adequate closure of the wound, this major catastrophe has been eliminated in a large number of gall-bladder operations which have been performed within the past 2 years in my clinic.

REFERENCES

1. Bowen, A. Am. J. Surg., 1940, 47: 3.
2. Kraissl, C. J., Kesten, B. M., and Cimiotti, J. G. Surg. Gyn. Obst., 1938, 66: 628.
3. Sokolov, S. Vest. Chir., 1931, 65: 219. Abstracted in Internat. Abstr. Surg., Surg. Gyn. Obst., 1932, 55: 157.

PAPILLARY CYSTADENOMA LYMPHOMATOSUM (WARTHIN'S TUMOR) OF THE PAROTID SALIVARY GLAND

HAYES MARTIN, M.D., F.A.C.S., and HARRY E. EHRLICH, M.D., New York, New York

PAPILLARY cystadenoma lymphomatosum does not constitute a serious or complicated problem in a tumor clinic. These benign tumors cannot be differentiated from mixed tumors of the parotid by clinical examination alone, and, in most cases, a specific diagnosis is not made until after a surgical specimen has been examined. Nevertheless, papillary cystadenoma lymphomatosum makes up a definite percentage of all parotid tumors, and, when the surgeon receives the histologic diagnosis from the pathologist, he will be called upon to give the prognosis and his recommendations as to the necessity for further care and follow-up examinations.

The present study was undertaken to determine the clinical behavior of these tumors and is based upon a series of cases of papillary cystadenoma lymphomatosum culled from the records of 359 parotid tumors, all observed in the Head and Neck Service of the Memorial Hospital from 1932 to March, 1944, inclusive.

Definition. The term, "papillary cystadenoma lymphomatosum," as used in this paper, designates an essentially benign cystic tumor occurring either in, or attached to, the parotid salivary gland. Its microscopic appearance is characterized by specific epithelial structures supported by a lymphoid stroma.

Other terms, that have been employed to designate this neoplasm, are adenolymphoma, branchiogenic adenoma, epitheliolymphoid cyst, branchioma, cylindrocellular branchiogenic adenoma, orbital inclusion adenoma, and onkocytoma.

In 1910, Albrecht and Arzt first established this tumor as a distinct morphologic entity. There have since been reported 66 genuine cases exclusive of the present series. In 1929, Warthin discussed the cases already in the literature and added 2 of his own. He gave an excellent description of their pathology and, from then on, the growth has often been referred to as Warthin's tumor, an eponym hardly justified from the standpoint of precedence. Although the term papillary cystadenoma lymphomatosum, contributed by Albrecht and Arzt, is reasonably accurate from a descriptive standpoint, nevertheless, it has the disadvantage of being long and cumbersome so that the figurative designation of Warthin's tumor, already in common usage, will probably continue to be employed as a matter of convenience.

From Head and Neck Service, Memorial Hospital, New York, New York.
Dr. Martin, attending surgeon; Dr. Ehrlich, Rockefeller Fellow in Cancer Research, Memorial Hospital.

ETIOLOGY

Incidence. Although papillary cystadenoma lymphomatosum is a somewhat uncommon neoplasm in general hospital admissions, it will be found to make up a definite percentage in large series of parotid tumors. On the Head and Neck Service of the Memorial Hospital, where about 1600 new patients with neoplasms are admitted yearly, 359 tumors of the parotid salivary gland (206 benign and 163 malignant) were observed during the period from January, 1932, to March, 1944, inclusive. The 22 cases of papillary cystadenoma lymphomatosum, herein reported, comprise 10 per cent of benign parotid tumors, 6 per cent of all parotid tumors, and less than 2 per cent of all neoplasms of the head and neck. This incidence is in accordance with the observations of Swinton and Warren, and others.

Age and sex. In this series, at the time of admission, the oldest patient was 73 years of age and the youngest was 30 years of age; the average age was about 53 years. There were 20 males and 2 females (ratio 10:1). This is in accordance with the observation of others that the tumor occurs characteristically in middle aged and elderly males. It is of interest to note that the 2 female patients, in our series, were 36 and 37 years of age, respectively, on

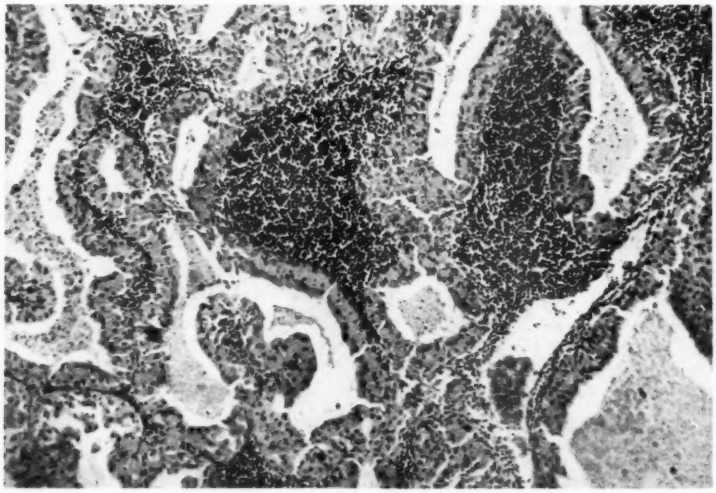

Fig. 1. General microscopic structure of papillary cystadenoma lymphomatosum, showing characteristic double layered epithelium, lymphocytic stroma, cystic pattern, and intracystic papillae.

admission as compared to the average of 53 years. The most likely explanation for this age-sex discrepancy is that the tumor tends to produce facial and cervical disfigurement early in its course, and females will, accordingly, seek consultation sooner. No satisfactory explanation has been advanced in regard to the predominance of papillary cystadenoma lymphomatosum in males. The incidence of salivary gland tumors, in general, is about equal in the two sexes.

The youngest patient whose case is described in the literature was a boy 2½ years of age, reported by Stoehr and Risak. The oldest patient was a male of 92 years, reported by Carmichael, Davie, and Stewart.

Causative factors. An analysis of our cases did not reveal any common causative factor. No history of trauma, previous infection, or calculous disease was obtained. The association of a papillary fibroma of the tongue (Case 2), nasal polyps (Case 6), lymphosarcoma of the neck and mediastinum (Case 8), capillary hemangioma of the face (Case 9), carcinoma of the stomach (Case 10), and ganglion of the wrist (Case 19), appeared to be merely coincidental.[1]

[1]All case numbers in this report refer to our series.

PATHOLOGY

Gross pathology. Cystadenoma lymphomatosum is an encapsulated tumor. The capsule is thin, strong, glistening, and is traversed by fine blood vessels. Rarely, however, the tumor may not be completely enveloped by a capsule, and, in such an instance, the neoplasm may infiltrate parotid substance for a short distance (Case 16). In our series, the specimens varied from 1.5 to 5.5 centimeters in greatest diameter, and were plumply ovoid and globular. The surface is either smooth, finely bosselated, or divided by branching clefts into pseudolobular pattern. The consistency is soft in some places, and fluctuant in others, although an occasional tumor may be firm throughout.

In most cases, when a Warthin tumor is opened, a chocolate-colored material, sometimes of mucinous appearance, exudes from the cut surface. When this material is scraped away with a knife, the tissue presents a glossy, or an opaque appearance, and the color varies from pink, to yellow, to brown. Most often, the cut surface is coarsely pseudolobulated, and contains several cysts varying from 1 millimeter to about 2 centimeters in diameter. These cysts are lined with shaggy tissue composed of papilliferous projections and some-

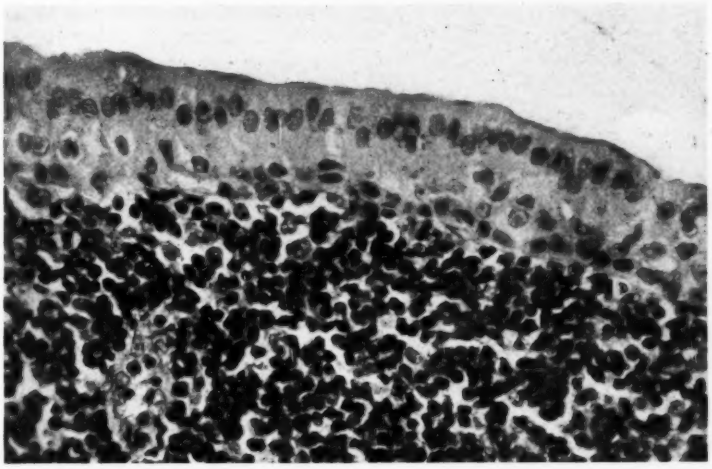

Fig. 2. High power microscopic appearance of the epithelium, in Warthin's tumor, showing an outer layer of tall columnar cells and a basal layer of cuboidal cells. The nuclei are large and coarsely granular; in the cylindrical layer, they are situated at the luminal end of the cells. The underlying lymphocytic stroma is abundant.

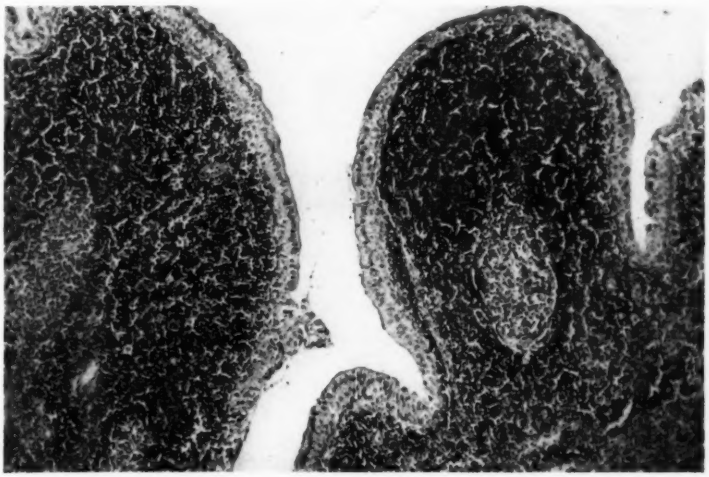

Fig. 3. Papillary cystadenoma lymphomatosum showing intracystic papillae which are covered by characteristic double layered epithelium. The lymphoid stroma contains fully developed germinal centers.

times the locules are completely filled with papillary tissue. The shaggy appearance of the lining of the cysts is the most striking naked eye characteristic of cystadenoma lymphomatosum. The papillary lining becomes more prominent after the specimen has been washed with water. Occasionally, a tumor is encountered whose cut surface is not multiloculated. The growth is often mottled by yellowish flecks and tiny areas of hemorrhage.

In our series, the growths were all situated beneath the fascia overlying the parotid gland

Fig. 4. Photograph (Case 19), showing a common location for papillary cystadenoma lymphomatosum (infra-auricular). This neoplasm was found to lie posterior to the tail of the parotid gland.

(deep cervical fascia), but the relation of the neoplasm to the gland was variable. In 9 cases, the tumors were superficial, but attached to the parotid capsule. In 7 cases, the neoplasms were found to lie beneath the parotid capsule and embedded within salivary gland tissue at varying levels. In 4 instances, the tumors were located posterior to the parotid gland, and, in these cases, it was necessary to elevate the tail of the parotid gland in order to expose the growth. There were 2 cases in which the growths were attached to the tail of the parotid gland, thus lying in the upper neck and in close relation to the superior pole of the thyroid gland. These tumors could easily have been mistaken for adenomas of the thyroid gland.

Although we could clearly demonstrate that the Warthin tumors, in our series, lay definitely in the parotid area, the growths often extended to involved adjacent structures, especially after attaining considerable proportions. In Case 14, the tumor was not only retromandibular and situated beneath the sternomastoid muscle, but it extended upward almost to the lateral wall of the pharynx. This neoplasm measured 5 centimeters in its greatest diameter, but was, nevertheless, completely encapsulated.

Histopathology. Papillary cystadenoma lymphomatosum is composed of tissue not found normally in the salivary glands, and its microscopic appearance represents a specific morphologic entity. It is characterized by papillary epithelial structures embedded in a lymphoid stroma. The papilliferous projections are covered by a peculiar eosinophilic, palisade-like epithelium, and, together with its supporting lymphoid stroma, are the most striking histologic features of this neoplasm (Figs. 1 and 3).

The general arrangement may be tubular, alveolar, or cystic, but is usually a combination of all three. The intracystic papilliferous projections vary from simple stalks or tufts to complex branchings. The spaces are lined by characteristic epithelium which is arranged in a double row of tall, evenly placed cylindrical cells resting on a thin basement membrane. The inner row of the cells is frequently cuboidal. Occasionally, a single row of cells is encountered, but the epithelium may also be heaped up. The cytoplasm is abundant, pale pink, and finely granular. The nuclei are large, most often spherical, but, occasionally, elongated and vesicular; they are situated at the luminal end of the cells (Fig. 2). The nuclei stain deeply, possess a distinct nuclear membrane and, very often, a large nucleolus. Warthin has maintained that the epithelium is ciliated, but; except for Robinson and Harless, no other investigator has been able to confirm this observation. Cilia were not demonstrated in any of our specimens. Many of the gland spaces contain a pink amorphous material, and some of the spaces are filled with débris and pycnotic nuclei.

The stroma may vary from scant lymphocytic infiltration (Fig. 3) to true lymphoid tissue containing fully developed germinal centers; the lymphoid stroma seems to be molded into the papillary stalks and tufts, and, at no time is it compressed or distorted by epithelial elements. This suggests that the

lymphoid element is an active part of the tumor. Occasionally, the lymphoid follicle may undergo partial, or complete hyalinization. Little connective tissue is seen, but, when present, it appears loose and relatively avascular. Not infrequently, broad sheets of hyalinized connective tissue are observed, especially in those tumors which contain scant lymphoid stroma.

The capsule, although thin, consists of dense fibrous tissue with an occasional bit of salivary gland tissue attached to it. No salivary glandular tissue was encountered within the tumor, nor was there any instance in which the tumor was found actually to invade the parotid gland. In Case 16, the growth was not completely encapsulated and, to the naked eye, appeared to infiltrate the parotid gland for a short distance; microscopic examination, however, did not reveal true invasion of the gland by tumor tissue.

A histologic variant, in our series, occurred in Case 7 in which atypical areas were seen. In many places, the epithelium was heaped up, and there was a loss of orientation between the epithelium and stroma, but true malignant transformation was not observed in any section. The only reported instance of anatomic malignant transformation is by Ssobolew. Notwithstanding, in our opinion, the submitted evidence, in this case, is not convincing, and does not justify a diagnosis of malignant papillary cystadenoma lymphomatosum.

Jaffé has described secretion capillaries between the epithelial cells with evidence of secretory activity and attributed the transformation of dilated glands into cysts to this secretion phenomenon. This has been confirmed by Freshman and Kurland, and by Wood. Staining techniques for the demonstration of intercellular capillary spaces were not carried out in any of our specimens.

Histogenesis. Many sources have been suggested to account for the origin of papillary cystadenoma lymphomatosum, including branchial arches, parotid lymph nodes, eustachian tube, oncocytic cells, "orbital inclusion," and embryonal buccal ectoderm. It has even been suggested by Lecène and Brachetto-Brian that the growth represented the development of an ectopic tonsil. While no single

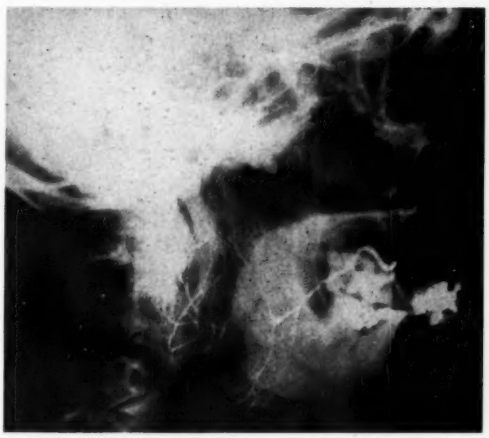

Fig. 5. Sialogram in Case 5. The ductal system of the parotid gland has been distorted due to extrinsic pressure produced by Warthin's tumor. Note large central defect and whorl-like appearance on the periphery.

hypothesis has been advanced which satisfactorily explains the genesis of the neoplasm, the various theories of histogenesis are briefly described in the following paragraphs.

1. *The branchiogenic theory* was first proposed by Ssobolew, and has been favored by Askanazy, Rickl, Ewing, and others. These observers contend that the tumor has its origin from the ectodermal portion of a branchiogenic arch, because of its resemblance to the embryonal type of epithelium and lymphoid stroma found in the ordinary branchiogenic cyst. Furthermore, its epithelium has been said to resemble the eosinophilic cells of the parathyroid glands. No convincing evidence, however, has been furnished to support this hypothesis.

2. Warthin suggested that the tumor might arise from heterotopic pharyngeal ectoderm, possibly the *eustachian tube*, and he has been supported by Wendel. This theory, too, is based on similarities in the epithelium.

3. According to Kraissl and Stout, a definite structure—the *orbital inclusion*—which gives rise to the orbital salivary glands in certain carnivora appears as a vestigial rudiment in human embryos. During the growth of the embryo, the parotid gland comes to lie in close proximity to this vestigial epithelial lymphoid structure whose lining cells are supposed to

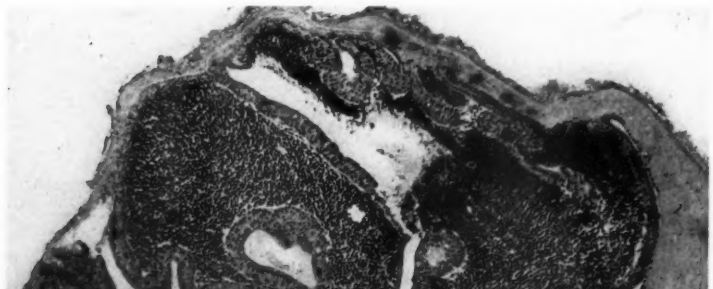

Fig. 6. Aspiration biopsy of papillary cystadenoma lymphomatosum (paraffin section of a plug of tissue), showing characteristic epithelium and lymphoid stroma.

resemble the epithelium of cystadenoma lymphomatosum. These investigators maintain that the probable origin of the tumor is from a dilation and proliferation of the orbital inclusion. This theory is attractive in that it tries to account for the lymphoid as well as the epithelial elements of the tumor, for most authors agree that the lymphocytic tissue takes an active part in the formation of the neoplasm. One objection to this hypothesis is that the orbital inclusion has been demonstrated in man.

4. The theory, that the tumor arises from *heterotopic salivary gland rests* situated in lymph nodes adjacent to the parotid gland, was first expressed by Albrecht and Arzt. This hypothesis (derivation from heterotopic rests) tends to support the morphologic impression that the lymphoid component is part of the growth and does not represent remnants of a lymph node. It also explains, in part, why the tumors may be encountered within, or attached to, the parotid salivary gland. Anatomic evidence has been submitted to support this theory. Neisse has described lymph nodes in the parotid gland of a 120 millimeter fetus which contained salivary tubules. He has also demonstrated salivary tissue within preparotid lymph nodes of newborn infants. These observations have been confirmed by Nicholson (18, 19), Bunting and Tennant (quoted by Plaut), and others. Lang claims to have encountered salivary acini and tubules in cervical lymph nodes. Ewing (quoted by one of us—MM., 16) has observed remnants of glandular acini in cervical lymph nodes which he interpreted as embryonal rests.[1] Since there is reasonable anatomic basis to support the contention that areas of salivary tissue may become enclosed in parotid and preparotid lymph nodes during development of the gland, the hypothesis that cystadenoma lymphomatosum is derived from these heterotopic rests appears to be the most acceptable, but not completely satisfactory explanation for the genesis of this tumor. The main objection to this theory is that conclusive evidence has not been offered to indicate that the lymphoid tissue is part of

[1] In a paper recently published by one of us, there was some discussion as to the histogenesis of branchiogenic carcinoma and the possibility of primary carcinoma arising in cervical lymph nodes. In that paper, we quoted Stewart (personal communication) to the effect that he had never observed any cellular elements in normal cervical lymph nodes which he could interpret as being of epithelial origin. He suggested that, since lymph nodes are normally present within the parotid and submaxillary glands, histologic preparation might show glandular tissue adhering to, or as artefacts appearing within, such lymph nodes. In that paper, we were concerned mainly with the possibility of epidermoid carcinoma arising primarily from cellular rests in cervical lymph nodes. Stewart's observations would probably hold true for adults and for epidermoid rests in cervical lymph nodes separate from the parotid glands, but, nevertheless, the evidence seems clear that several investigators have demonstrated glandular epithelial remnants identical with salivary acini and ducts embedded within parotid and preparotid lymph nodes of human fetuses and children.

a lymph node; lymph sinuses were not encountered in any of our specimens, nor have they been demonstrated by other investigators.

5. A variation of the theory of Albrecht and Arzt has been proposed by Hamperl, and is based on the presence of certain characteristic cells found in the salivary glands which appear by a process of differentiation from both glandular and duct epithelium. They contain a finely granular cytoplasm, their nuclei are indented and rich in chromatin, and they have even been reported to form hyperplastic nodules. These cells, which were first called pycnocytes, but, later, named oncocytes by Hamperl, are supposedly encountered more frequently in individuals over 30 years of age, and almost constantly during and after the 6th decade. Jaffé, who contributed the term "onkocytoma" for this tumor, has developed the thesis that the growth has its origin from oncocytes in aberrant salivary tissue of lymph nodes adjacent to the parotid gland.

SYMPTOMS AND CLINICAL COURSE

Papillary cystadenoma lymphomatosum is presumably always a rather slow growing tumor, that is, it does not reach a size of several centimeters in less than a year, usually more. The rate of growth is slow and steady up to a size of 4 to 5 centimeters when further growth has a tendency to be self-limited. In our series, the patients who gave short histories all admitted that the tumor was at least 2 centimeters when first discovered. The shortest stated duration of the tumor before admission was 2 months, and the longest, 12 years. It is probably somewhat coincidental that about one-quarter of our patients gave exactly 3 years as the duration of the tumor. In 50 per cent of the cases, the duration of the tumor was more than 1 year. The average duration of 3 years is somewhat shorter than that of benign mixed tumors (6½ years) as observed in our clinic. In only 2 cases was there a history of rapid growth—in the cases of 2 patients with tumors of 4 centimeters in diameter who stated that the masses had been present only 6 to 8 months, respectively. Carmichael, Davie, and Stewart reported a case which was present for more than 30 years before excision was carried out.

Most of the patients, in our series, complained of no symptom other than cervical or facial disfigurement. In only 2 cases, was there a history of slight pain at the tumor site associated with recent rapid growth and possibly due to a more rapid accumulation of fluid within the cystic mass. The average patient with papillary cystadenoma lymphomatosum seeks medical advice either because of the unwelcome deformity of the growing tumor or apprehension as to its true nature. The time of seeking medical advice is usually selective.

In our cases, the tumors were located most frequently in the midportion of the parotid, or, in other words, just in front of the lobule of the ear. In 13 cases, the tumors occurred around the borders of the parotid, particularly at the tail of the gland; that is, just behind and a little below the angle of the jaw or even in the upper neck. The tumors were usually single, ovoid, and sharply circumscribed, varying in size from 1.5 centimeters to 5.5 centimeters. In 3 cases, growth occurred bilaterally. There was one instance of homolateral multiple tumors (Case 22) and 1 case in which multiple tumors were encounted bilaterally (Case 20). The distribution between the two sites was about equal.

On clinical examination, the growths were all of smooth contour, only moderately firm, or even slightly fluctuant in consistency. The nodularity and marked induration, so characteristic of mixed tumors, is not found in papillary cystadenoma lymphomatosum. Except when located in the retromandibular portion of the parotid, these tumors are always movable and, even though they arise within the parotid in their progressive enlargement, they tend to migrate toward and lie on the surface of the gland as do other encapsulated tumors of the parotid. When papillary cystadenoma lymphomatosum arises in the retromandibular portion of the parotid, the growing tumor is compressed between the posterior edge of the ascending ramus of the mandible and the mastoid process, and the clinical findings will be mainly that of diffuse ill defined fullness of the parotid area due to expansion of the deep lying tumor.

Since the tumor is encapsulated and noninfiltrating, there is no change in the appear-

ance of the overlying skin. In our group, about 10 per cent of the cases were bilateral and 5 per cent homolaterally multiple. In the literature, we have found 2 cases of bilateral papillary cystadenoma lymphomatosum (Nino, and Oughterson, quoted by Plaut), but no previous instance of multiple homolateral occurrence of this tumor has been reported.

The clinical course of Warthin's tumor is essentially benign. In the 2 cases of longest duration, 7 and 12 years, respectively, there had been little change in appearance for the several years preceding the operation. The tumors tend to recur promptly following incomplete excisions, as was illustrated in Cases 7 and 12, and as reported by Carmichael, Davie, and Stewart. Malignant transformation did not occur in any of our cases, and we doubt the authenticity of the one instance reported in the literature.

In our series, the tumors were situated in, or attached to, the parotid salivary gland. Our records reveal no occurrence of this tumor in the lacrimal salivary glands, or in any minor salivary gland tissue. In the literature, there were 3 instances of Warthin's tumor reputedly occurring in the submaxillary gland by Albrecht and Arzt, Spitznagel, and Wendel. After a review of these references, it seems to us that these cases are not well authenticated. None of these authorities actually stated that the tumors were found in the substance of the submaxillary gland or attached to its anterior surface. The fact that they have not done so indicates that they have not appreciated the fact that the anteroinferior aspect of the tail of the parotid lies in contact with the posterior superior aspect of the submaxillary salivary gland, although the deep cervical fascia separates the two. Since papillary cystadenoma lymphomatosum can so consistently be demonstrated to arise or, at least, to lie in direct contact with the surface or borders of the parotid salivary gland, an error could easily be made from the standpoint of surgical pathology, if the tumor arose in the parotid at its point of contact with the submaxillary salivary gland. The fact that, in our series, none of the tumors arose separately from the parotid gland does not prove, of course, that they may not rarely do so. On the other hand, our series comprises one-quarter of all cases so far recorded and, furthermore, in our opinion, no conclusive evidence has, thus far, been advanced to indicate definitely the occurrence of Warthin's tumor other than in the parotid gland.

DIAGNOSIS

There are no clinical stigmas sufficiently characteristic of papillary cystadenoma lymphomatosum to distinguish it from certain other much more common tumors of the parotid. We have found no case reported in the literature with a preoperative diagnosis of this specific neoplasm and, in the present series, a clinical diagnosis was not made in a single instance before an aspiration biopsy report was returned or, failing that, before histologic examination of the surgical specimen. In our series, the preoperative diagnosis was made by aspiration biopsy in 12 cases as will be discussed later in this report.

Differential diagnosis. Since papillary cystadenoma lymphomatosum is, we believe, always located in the parotid area and possesses such characteristics of a benign growth as long duration, smooth contour, mobility suggesting encapsulation, and lack of infiltration, it will usually and logically be tentatively diagnosed by the experienced examiner as a mixed tumor.

In 4 of our cases, where the tumors appeared in the upper neck just on, or below, the tail of the parotid, the soft, fluctuant character led to the tentative diagnosis of branchiogenic cyst and, in 2 others of the cervical cases, the diagnosis of malignant lymphoma and adenitis, respectively, were made. Delanglade, Peyron, and Rouslacioix reported a case, in which a tentative diagnosis of carotid body tumor was made before operation, which seems to us rather farfetched on the basis of probability and dissimilarity in clinical findings.

There are no differentiating features to distinguish Warthin's tumor from a cellular mixed tumor of smooth contour, although, of course, no experienced surgeon would be in doubt as to the true nature of the nodular indurated variety of the mixed tumor. Metastasis from silent primary cancer in the mouth or upper portions of the pharynx may occur in lymph nodes situated in the upper portion of the neck or even overlying the parotid. It is

possible to confuse such lesions with tumors of parotid origin, especially if the possibility of silent primary cancer is not appreciated.

Other cystic tumors, which occur in the region of the parotid or in the upper neck, are cystic mixed tumors, cystic carcinoma of the parotid, and branchiogenic cysts, the latter often exhibiting walls thickened to 1 centimeter, or more, by lymphoid hyperplasia. As with cellular mixed tumors and lymphomas of the parotid lymph nodes, there are no distinguishing features and the diagnosis must be made either by aspiration biopsy or examination of the surgical specimen.

Sialography. Roentgen visualization of the parotid gland after the instillation of lipiodol into the ducts was carried out in 13 cases, following the technique of Blady and Hocker, and satisfactory sialograms were obtained in 12 cases. The general roentgenographic appearance produced by papillary cystadenoma lymphomatosum was not diagnostic or specific. The findings consisted mainly of slight displacement or distortion of part of the duct system. Since many of the tumors were merely attached to, rather than within, the parotid gland, appreciable sialographic changes were not to be expected. When the growths were embedded within salivary gland tissue, especially in the preauricular area, then a significant displacement of the finer ducts could be demonstrated (Fig. 5). Aside from frequently indicating that an encapsulated and probably benign tumor has produced extrinsic pressure on a certain portion of the duct system of the gland, sialography was of no great aid as a diagnostic procedure.

Aspiration biopsy (14, 15). This procedure was performed in 18 cases. In 12 cases, a report of papillary cystadenoma lymphomatosum was returned by Dr. Fred Stewart, pathologist of the Memorial Hospital. In 9 of these, a positive report was based on examination of a paraffin section of an aspirated plug of tissue (Fig. 6). A smear of aspirated material is less reliable in establishing a diagnosis of this specific neoplasm. Failure of the positive diagnosis from aspiration biopsy is largely due to the lymphocytic character of the tumor so that, in most cases, it is impossible to differentiate normal lymph nodes, malignant lymphomas, chronic adenitis, and Mikulicz's disease from Warthin's tumor. There were 5 cases in which aspiration biopsy was negative, in spite of the fact that the procedure was repeated in 3 of them.

If aspiration biopsy is to provide a high percentage of correct preoperative diagnoses in papillary cystadenoma lymphomatosum, or in most benign tumors, the pathologist must be familiar both with the clinical settings of the particular tumors, and with the kinds of tissue, together with the histologic variants likely to be found in the different types of benign tumors. Many times, the correct diagnosis depends on an intelligent guess on the part of the pathologist whose report may often read that the microscopic findings are merely "consistent with" the diagnosis of such and such a tumor.

TREATMENT

The treatment of papillary cystadenoma lymphomatosum is by surgery, the tumor being enucleated by sharp and blunt dissection along its capsular wall. Nothing is to be gained by a wider excision so as to include a margin of parotid tissue; as a matter of fact, such wide excision will almost always result in unnecessary injury to some of the branches of the plexus of the 7th cranial nerve. Extracapsular enucleation is also the proper treatment for other delimited tumors of the parotid, and, as such, need not be specifically selected for Warthin's tumor. In any case, deliberate selection of treatment for this particular tumor would not be possible, except after a positive aspiration biopsy.

Surgical excision of non-infiltrating encapsulated parotid tumors should always be carried on without too great a period of delay. Under a waiting policy, many mixed tumors of the parotid will undergo malignant transformation and metastasis. In obviously benign encapsulated parotid tumors, there is nothing to be gained by waiting, and, should the growth be a mixed tumor, then malignant transformation with metastasis may occur before there is any particular indication for operation. If all non-infiltrating encapsulated parotid tumors were treated according to this plan, then Warthin's tumor would, of necessity, be included

TABLE I.—PAPILLARY CYSTADENOMA LYMPHOMATOSUM—TABULATION OF 22 CASES

Case No. Initials Age Sex	Date of admission	Topographic location	Duration	Greatest diameter cm.	Aspiration biopsy	Involved portion of parotid gland	Treatment	Follow-up period without recurrence	Remarks
1 W.R. 49 M	2- 5-32	Right preauricular	3 mo.	2	Not done	Central (just beneath parotid fascia)	Excision	12 yrs.	Not in parotid substance
2 G.M. 47 M	3-25-35	Left infra- and retromandibular	1 yr.	1.5	Not done	Tail (behind sternocleidomastoid muscle	Excision	9 yrs.	Resembled enlarged cervical lymph node
3 G.K. 36 F	5-11-35	Left preauricular	1 yr.	3.5	Negative	Central	Excision	9 yrs.	.....
4 R.C. 73 M	11-25-36	Left preauricular	3 yrs.	5.5	Negative, 1st Positive, 2nd	Central	Excision	5 yrs.	Died 4-1-41 coronary thrombosis
5 W.K. 51 M	2-24-37	Right retromandibular	1 yr.	4	Positive	Tail	Excision	7 yrs.	.....
6 I.I. 41 M	5- 9-37	Left retromandibular	6 mos.	2.5	Negative	Tail	Excision	7 yrs.	Adjacent to parotid gland
7 J.L. 64 M	7-31-39	Right retromandibular	3 mos.	3	Not done	Central	Not excised because of rectal bleeding	Regressed after 2 yrs.	Recurrent case (incomplete excision 1930)
8 B.R. 54 M	8-27-39	Right preauricular	1 yr.	3.5	Lymphoid infiltration of parotid	Central (just beneath parotid fascia)	Excision	5 yrs.	Also had lymphosarcoma
9 C.O. 58 M	1- 4-40	Right preauricular	3 yrs.	4	Negative (twice)	Central (just beneath parotid fascia)	Excision	4 yrs.	.....
10 T.E. 66 M	3-11-40	Carotid bifurcation (right)	3 yrs.	5	Positive	Posterior to tail	Excision	4 yrs.	Presented as neck tumor
11 J.L. 53 M	3-26-40	Left retro- and inframandibular	6 mos.	4	Positive	Posterior to tail	Excision	4 yrs.	.....
12 R.S. 37 F	5- 7-40	Right infraauricular	1 yr.	3	Negative (twice)	Tail	Excision following 1½ years' observation	4 yrs.	Second recurrence following incomplete excision elsewhere (Initial tumor 7 years duration)
13 E.M. 69 M	9-10-40	Right inframandibular	3 yrs.	3	Not done	Tail	Excision	1¾ yrs.	Presented as a neck tumor. Died June, 1942, stomach cancer
14 J.F. 47 M	a) 1-26-41	Right infraauricular & inframandibular	1½ yrs.	5	Not done	Posterior to tail	Excision	3 yrs.	Posterior to sternocleidomastoid muscle, extended to wall of pharynx. Presented as cyst of neck
	b) 4- 6-43	Left retromanibular	6 mos.	3	Positive	Attached to tail	Excision	1 yr.	Bilateral case
15 H.K. 64 M	2-23-41	Posterior to left angle of right mandible	8 mos.	4	Positive	Adjacent to tail	Excision	3 yrs.	Presented as a neck tumor
16 A.V. 61 M	7- 1-41	Left retro- and inframandibular	3 yrs.	4	Negative (twice)	Tail (deeply embedded)	Excision	2½ yrs.	Upper portion not encapsulated appeared to infiltrate gland for short distance
17 C.R. 54 M	3- 1-42	Right infraauricular	6 mos.	4	Positive	Posterior to tail	Excision	2 yrs.	.....
18 R.B. 30 M	8-12-42	Left preauricular	3 yrs.	3	Not done	Central (beneath parotid capsule)	Excision	1½ yrs.	.....
19 J.A. 47 M	2-27-43	Left preauricular	12 yrs.	4.5	Positive	Posterior to tail	Excision	1 yr.	.....

TABLE I.—PAPILLARY CYSTADENOMA LYMPHOMATOSUM—TABULATION OF 22 CASES—Continued

Case No. Initials Age Sex	Date of admission	Topographic location	Duration	Greatest diameter cm.	Aspiration biopsy	Involved portion of parotid gland	Treatment	Follow-up period without recurrence	Remarks
20 L.L. 60 M	8- 6-43	Right infra-auricular	3 yrs.	2	Positive	Tail (just beneath capsule)	Excision	9 mos.	Bilateral case—multiple tumors in both parotid glands
		Left infra-auricular	2½ yrs.	5	Positive	Tail (just beneath capsule)	Excision		
21 B.T. 67 M	1-14-44	Right infra-auricular and retromandibular	?	2.5	Positive	Posterior to tail	Excision	4 mos.	.....
22 R.C. 46 M	2-16-44	Pre- and infra-auricular (both sides)	2 mos.	3	Positive	Lower pole (both sides)	Excision	3 mos.	Bilateral case—multiple tumors in left parotid gland

and the diagnosis established on histologic examination. Most patients will prefer to have removed those tumors which cause appreciable facial deformity, or asymmetry, especially if there is progressive growth. If the diagnosis of papillary cystadenoma lymphomatosum has been clearly established by aspiration biopsy and the patient is greatly opposed to operation, the surgeon need have little fear that the tumor will undergo malignant transformation. The one reported instance of such an occurrence, Ssobolew, is not, in our opinion, authentic. Even though the tumors grow to be a fairly large size, they do not infiltrate the parotid and endanger the 7th nerve so that excision can be safely delayed.

All tumors in the present series were surgically excised with the exception of that of Case 7; in this instance operation was deferred because of severe anemia secondary to chronic rectal bleeding. Except for Case 16, in which the growth had apparently extended through its capsule and become densely attached to the parotid, all the tumors were completely encapsulated, and were enucleated with ease.

The surgical approach and technique of enucleating Warthin's tumors are identical with that of operations for encapsulated mixed tumors, and will not be discussed in any detail here. In brief, when the tumor lies at the edge of or within a short distance of the outer surface of the parotid gland, the best method of approach is by a straight incision directly over the surface of the tumor in a radial direction from the attachment under the lobule of the ear. Incisions so placed can be carried fairly deeply into the substance of the parotid gland and, with care, no branches of the facial nerve will be severed. The edges of the wound can then be widely retracted without placing any undue tension on the branches of the 7th nerve for the reason that the incision is in the general direction parallel with the nerve branches. Once the dissection is carried through the subcutaneous tissues and the capsule of the tumor is encountered, the growth may be freed from its bed by blunt dissection with a minimum of trauma to the parotid gland and branches of the 7th nerve.

When the tumors arise in the retromandibular portion of the parotid, the safest approach is through a Y-shaped incision, one branch running upward on the aspect of the lobule and the tragus, a second running up behind the ear close to the reflection of the skin over the mastoid, and the third running downward along the upper anterior border of the sternomastoid. After these incisions are deepened, the lobule of the ear is reflected upward and the anterior and posterior flaps are retracted, thus exposing the upper anterior border of the sternomastoid muscle and the mastoid process. The dissection should then be carried down between the anterior aspect of the mastoid process and the parotid until the main trunk of the 7th nerve is exposed. After the nerve has been demonstrated, the operation can proceed safely without danger of nerve injury, and the tumor can be enucleated by blunt dissection along its capsule.

In our series, no technical difficulties were encountered except in one instance in which a retromandibular tumor extended inward to

the wall of the pharynx. In this case, there was temporary paralysis of the 7th nerve due to stretching and manipulation with eventual complete recovery.

Radiation therapy. Inasmuch as the tumor contains abundant lymphocytic components, the question as to its possible radiosensitivity and a preference for radiation therapy might be raised. On the other hand, the character of the lymphoid tissue, the presence of the adenoid elements, and the cyst formation, do not augur well for the success of radiation therapy. It has been fairly definitely established that hyperplastic lymphoid tissue, in general, is not highly radiosensitive and will not regress under irradiation unless the dosage is high. The question is of little practical import, however, since the results of surgery are so expeditious and satisfactory as to leave almost no indication for any other method of treatment. We have few data as to the effects of radiation therapy in our series. We, ourselves, did not employ it. In one of our cases, the patient was referred following the application of 1250 r of roentgen therapy (other factors not available) 6 days following an alleged complete excision of a Warthin's tumor. Shortly after this treatment, there was an apparent recurrence for which the patient was referred to our clinic, but the poor physical condition from anemia, due to rectal hemorrhage, precluded surgical excision. The patient was followed at regular intervals, and, at the end of the year, was lost to follow up. Several features in this case are so uncertain that we do not think any conclusions should be drawn from it. So far as the literature is concerned, there is no evidence relative to the radiosensitivity or radiocurability of this specific tumor.

Recurrences. In our series of 21 surgical excisions, there have been no local recurrences to date. The tumor does recur, however, if not completely excised. Drainage of the cyst is not sufficient. In 2 of our cases, there had been incomplete excisions before admission. In 1 case, the tumor had been operated upon twice, 1 year and 1 month, respectively, before admission to the Memorial Hospital. After complete excision of the tumor, in our clinic, the patient has remained free from recurrence for 4 years.

PROGNOSIS

Based on past experience with this tumor, papillary cystadenoma lymphomatosum is considered a benign neoplasm in the Head and Neck Clinic at the Memorial Hospital. The tumor has never recurred following local excision in our clinic. We have found no suggestion of malignant transformation in any excised specimen even after repeated incomplete surgical excisions. No conclusive instance of a malignant Warthin's tumor has been reported in our literature.

END-RESULTS

With one exception (Case 7), all of our patients have been seen at regular intervals—the follow-up periods varying from 6 months to 12 years from the date of admission. Six cases have been followed for 5 years or more, and 6 cases have been followed from 3 to 5 years. One patient died of coronary thrombosis 5 years following excision of a cystadenoma lymphomatosum and another succumbed to gastric cancer 20 months after operation for this specific salivary gland tumor. In Case 8, the patient also had reticulum cell lymphosarcoma of the neck and mediastinum; this associated neoplastic disease has been controlled satisfactorily with high voltage roentgen therapy for a period of 5 years.

SUMMARY

Twenty-two cases of papillary cystadenoma lymphomatosum of the parotid salivary gland are reported and analyzed. The histogenesis of the tumor has not been definitely established. There is a reasonable anatomic basis to support the theory of its origin from heterotopic salivary gland rests situated in lymph nodes adjacent to, or within, the parotid gland.

The neoplasm is a distinct morphologic entity, but it cannot be distinguished clinically from the relatively common mixed parotid tumor. Cystadenoma lymphomatosum recurs promptly if surgical excision is not complete. All tumors in this series were automatically and clinically benign. There are no satisfactory data to indicate whether these tumors are radiosensitive or radiocurable.

Since the conclusion of this study, 3 additional patients with cystadenoma lymphomatosum of the parotid gland

were treated on the Head and Neck Service. The data accumulated in these cases in no way alter the clinical and anatomic observations here recorded.

REFERENCES

1. Albrecht, H., and Arzt, L., Frankf. Zschr. Path., 1910, 4:47.
2. Askanazy, in Henke, F., and Lubarsch, O. Handbuch der speziellen pathologischen Anatomie und Histologie. Vol. 1, part 1, p. 333. Berlin: Julius Springer, 1926.
3. Blady, J. V., and Hocker, A. F. Surg. Gyn. Obst., 1938, 67:777.
4. Brachetto-Brian, D. Bol. Soc. cir. B. Aires, 1931, 15:718.
5. Carmichael, R., Davie, T. B., and Stewart, M. J. J. Path. Bact., Lond., 1934, 40:601.
6. Delanglade, Peyron, and Rouslacioix. Bull. Ass. fr. cancer, 1914, 7:370.
7. Ewing, James. Neoplastic Diseases. 4th ed., p. 798. Philadelphia: W. B. Saunders & Co., 1914.
8. Freshman, F. W., and Kurland, S. K. Am. J. Clin. Path., 1938, 8: 422.
9. Hamperl, H. Virchows Arch., 1931, 282: 724.
10. Jaffé, R. H. Am. J. Cancer, 1932, 16: 1415.
11. Kraissl, C. J., and Stout, A. P. Arch Surg., 1933, 24: 485.
12. Lang, F. J., in Henke, F., and Lubarsch, O. Handbuch der speziellen pathologischen Anatomie und Histologie. Vol. 5, part 2, p. 128. Berlin: Julius Springer, 1929.
13. Lecène, P. Rev. Chir., Par., 1908, 37: 1.
14. Martin, H. E., and Ellis, E. B. Am. J. Surg., 1930, 96: 169.
15. Idem. Surg. Gyn. Obst., 1934, 59: 579.
16. Martin, Hayes, and Morfit, H. Mason. Surg. Gyn. Obst., 1944, 78: 133.
17. Neisse, R. Anat. Hefte., 1898, 287.
18. Nicholson, G. W. Guy's Hosp. Rep., Lond., 1922, 72: 333.
19. Ibid., 1923, 73: 37.
20. Niño, F. L. Bol. clin. quir., univ. Buenos Aires, 1940, 16: 271.
21. Plaut. J. A. Ann. Surg., 1943, 116: 43.
22. Rickl, A. Zbl. allg. Path., 1924, 35: 310.
23. Robinson, D. W., and Harless, M. S. Surg. Gyn. Obst., 1943, 76: 449.
24. Spitznagel. Wien. klin. Wschr., 1929, 2: 983.
25. Ssobolew, L. W. Frankf. Zschr. Path., 1912, 11:463
26. Stoehr, F., and Risak, E. Arch. klin. Chir., 1926, 143: 609.
27. Swinton, N. W., and Warren, S. Surg. Gyn. Obst., 1938, 67: 424.
28. Warthin, A. S. J. Cancer Research, 1929, 13:116.
29. Wendel, A. J. Cancer Res., 1930, 14: 123.
30. Wood, D. A. Am. J. Path., 1935, 11: 889.

COLOR MATCHING OF SKIN GRAFTS AND FLAPS WITH PERMANENT PIGMENT INJECTION

GERTRUDE HANCE, and JAMES BARRETT BROWN, M.D., F.A.C.S.,
LOUIS T. BYARS, M.D., F.A.C.S., FRANK McDOWELL, M.D., F.A.C.S., St. Louis, Missouri

TEN years ago Dr. Vilray P. Blair suggested to us the idea of coloring skin grafts so they would match the surrounding tissues. This suggestion and his constant encouragement are responsible for the results we have obtained.

Of necessity free skin grafts and pedicle flaps are often employed about the face to reconstruct features (Fig. 1), replace surface lesions (Fig. 2), or relieve distortion resulting from scar (Fig. 6). Full thickness skin grafts from behind the ear or forehead flaps usually result in reasonably good color matches with face skin; but with grafts and flaps from other areas there is often a color contrast that detracts from an otherwise good result. This transplanted skin may be lighter or darker than that of the recipient area and may more strikingly lack the red tones of the face skin. Women may use makeup to hide such contrasts, but men often refuse to use it.

This problem of contrasting color can be largely overcome by introduction of permanent pigments into the transplanted skin to create a color match with the recipient area.

There is archaeological evidence to show that tattooing of the skin dates as far back as 4000 to 2000 B.C. at which time it was practiced in Egypt. The first records of this practice in Southern China date 1100 B.C. Through the ages there have been various reasons for marking the skin. The Greeks and Romans used this method to mark prisoners of war, criminals, and slaves. It is practiced now for personal adornment and to establish religious, family, or tribal markings. Some modern work has been reported on the tattooing of disfiguring white corneal scars;[1] the method has had limited use in making dark skin blemishes less noticeable by injecting lighter colors.

From the Department of Surgery, Washington University School of Medicine, Saint Louis, Missouri.

[1]Surgery of the Eye. By M. Weiner, and B. Y. Alvis, Philadelphia: W. B. Saunders Co., 1939.

On the basis of the cautious use of the procedure over 8 years of time, it is felt that worthwhile results can be obtained with transplanted skin to heighten the perfection of surgical repairs.

Tattooing is the practice of pricking the skin with needles and carrying into the skin and depositing various pigments. Such pigments should be nonpoisonous, stable to light, nonirritating to the skin, and stable to the prolonged effect of tissue metabolism. Extreme insolubility is thus essential. Among the pigments used are the following:

1. White — Barium sulphate is extremely insoluble. It is used in color blending in most instances.

2. Yellows and browns—These come from the ochers, the earthy metallic oxides, and vary in shades from light yellow to brown and red. The color is controlled by the amounts of hematite and limonite present. The shades are controlled by the material mixed with this; these materials are clay, chalk, or gypsum. Artificial ochers, yellow and brown, are produced in probably a more pure state by precipitation of iron salts. The artificial red ochers are produced by roasting the natural yellow and brown ochers, causing them to lose water and be converted into iron oxides. This produces light red, burnt ocher and a yellowish-red shade. Umber, a brown ocher, owes its color to the presence of manganese.

3. Black — This is carbon; it is used considerably in color blending.

4. Red—In addition to certain of the ochers alizarin, synthetic or from madder, is used.

TECHNIQUE

The area is prepared with soap and water and alcohol. It must be free from infection. The instruments are sterilized; the pigments may be autoclaved each time, or kept as a sterile stock supply.

a b c

Fig. 1. a, Reconstruction of portion of nose from arm flap. The columella has not yet been attached to the lip. A portion of this flap was injected while still on the arm and the contrast with the uninjected portion is easily seen. This seemed to work satisfactorily in this case. However, if much shrinkage of such a flap occurred there might be condensation of pigment and a resulting dark color. b, Result of recent color injection. There is still some mottling. c, Final result 7 months after color injection. The mottling has disappeared and color match is good.

Oftentimes sensation in the area to be treated is diminished; otherwise local block anesthesia is most desirable. Infiltration anesthesia can be used but interferes somewhat with skin texture and color.

With a spatula the dry colors are mixed thoroughly on a clear glass slab and moistened with normal saline until about the consistency of thick cream. For matching a graft to the face skin, one starts with small amounts of red, yellow, and white. The correct mixture will be a shade darker than the skin. Spreading a thin coating of the trial mixture over the skin to be injected helps in obtaining a match. Its color is lightened somewhat by the white of the skin. It is better to err on the side of too light a color as this may be darkened later if necessary.

It is impossible to designate exact amounts of pigment to use in mixing because of the variation in pigments as well as normal differences in skin. Often after the red, yellow, and white are mixed to the desired shade, a small drop of black is added to give the tone of the skin.

The instrument for injecting the pigment consists of one or several fine needle points attached to a handle which is held like a pencil. These points, if of more than one needle, are set in a single row and soldered in place. The pigment is picked up on these points and the needle inserted obliquely into the skin. The needle pricks are very close together. Professional tattooers use an electrical vibrator to move the needle points up and down. After a great deal of experience such an instrument would enable one to proceed more rapidly.

The excess pigment is constantly wiped from the skin surface so that the evenness of injection may be observed. The pigment is deposited along the channel of the needle, most of it being in the outer two-thirds of the skin.

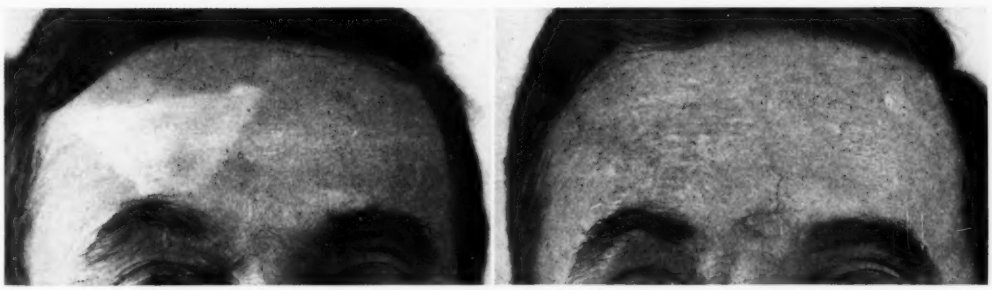

Fig. 2. a, left, Completely white skin graft on forehead. b, Result obtained soon after color injection. The mottled appearance disappears as the pigment diffuses slightly with time.

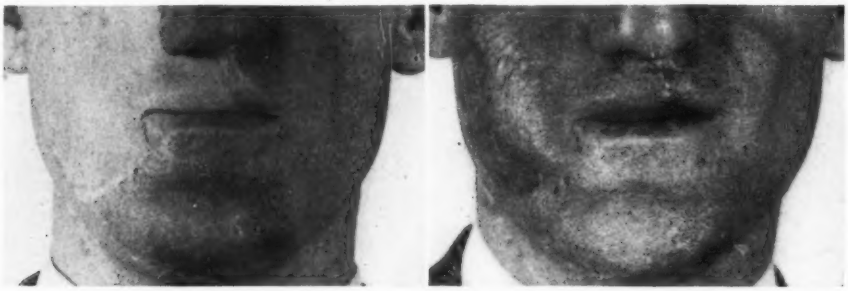

Fig. 3. a, left, Massive repair of face, lip, and orbit with flap from the chest for defect resulting from an explosion. Color differential and absence of vermilion are very marked. b, Color injection to simulate vermilion, and match color of cheek. There is still some swelling and peeling of the skin present.

Fig. 4. a, left, Destruction of vermilion of upper and border of lower lip from lye burn. An arm flap repair of border of lower lip has been done. The lining of the lower lip is entirely constructed with arm flap, that of the upper lip with free skin graft. When lipstick is smeared the absence of underlying color is doubly obvious. b, Simulation of both upper and lower vermilion by pigment injection.

The skin appears pale immediately after the injection. This is followed by a period of inflammation lasting a week or 10 days. Following this, there is peeling of the skin (Fig. 3). During the period of inflammation vaseline or sulfathiazole ointment is applied.

The color gradually diffuses and pales somewhat (Figs. 1 and 2). Patchy areas may appear. A second treatment is often needed, at which time color discrepancies can be corrected and patchy areas blended.

CHOICE OF CASES

Hard scarring interferes with the process of insertion and distribution of the pigment. Areas of no pigmentation or soft white scars are amenable. In such scarred areas the skin is not normal, thin scar epithelium being present, the derma thin or absent. Here the pigment must be inserted deeper in relation to the skin than in more normal situations.

Skin grafts. It is desirable that the graft be old enough to have achieved the greater part of its relaxation and resemble normal skin as nearly as possible. The graft which is dead white is ideal (Fig. 2). Yellowish and brownish tints to the graft are not serious drawbacks if this is considered in the blending of the pigments for injection. Occasionally, a deeply pigmented brown or greenish-brown graft is seen, sometimes when the patient has subjected it to sunlight in an effort to improve its color. It is difficult to lighten the color of such an area by pigment injection.

Skin flaps. These are more commonly used in the reconstruction of a feature such as the

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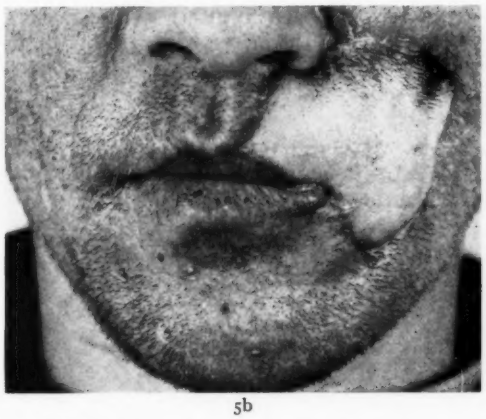

5b

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Fig. 5. a, Forehead flap in place to reconstruct one-third of the full thickness of the upper lip and a portion of the cheek. The absence of vermilion makes the repair look very artificial. b, Completion of the repair with vermilion simulated by pigment injection. This patient has a very dark complexion, and the forehead flap did not match the surrounding tissues as well as usual. c, Final result 6 months after color injection into the flap. The absence of beard was camouflaged by stippling with a brown-black mixture. The simulated vermilion is indistinguishable from the normal except on close examination.

nose, ear or full thickness of the lip or cheek (Figs. 1 and 5). The color is more likely to be dead white or yellowish than too dark. The texture is better and there is less superficial scarring than in the free graft and pigment injection may be done more easily.

Vermilion of the lip. Regardless of the perfection of contour of a lip reconstruction, with-

Fig. 6. a, left, Skin grafts of lower eyelids and nose much lighter in color than surrounding skin. Outer portion of eyebrows missing. b, Three months after matching of grafts to surrounding skin by pigment injection and simulation of brows by similar process. Because of diffusion of pigments stippling may be too coarse to simulate individual hairs.

out a vermilion the result is very imperfect (Figs. 3, 4, and 5). Lipstick is not entirely adequate because if smeared the underlying absence of vermilion is quite noticeable. Color injection of the border of such a flap reconstruction can reproduce the appearance of the normal vermilion very accurately and adds considerably to the adequacy of the repair. Surgical methods are often inadequate for this portion of the repair.

Bald spots within bearded areas are noticeable, but stippling with black has not been an entirely satisfactory disguise (Fig. 5). Black pigment is likely to appear bluish under the skin and must be used with care. Because of the diffusion of pigments the stippling is likely to be too coarse to simulate individual hairs and may produce a dirty appearance. Bald areas in the eyebrow may be disguised fairly well (Fig. 6).

CONCLUSIONS

Over a period of 8 years the injection of pigment into the skin has been used in 27 instances to match the color of free skin grafts to surrounding facial skin. This method has been used 8 times for the same purpose on skin flaps. It has been used in 10 instances to simulate missing vermilion of the lip. The appearance of the surgical repair has been definitely improved in every case, sometimes markedly so. There have been no complications or bad results from the procedure.

A TECHNIQUE OF ASEPTIC OR CLOSED GASTRIC RESECTION USING THE FURNISS CLAMP

LEO C. CULLIGAN, M.D., F.A.C.S., Minneapolis, Minnesota

IT is safe to say that more progress has been made in the reduction of mortality following resection of the stomach during the past 5 years than had been accomplished during the previous 25 or 30 years. This improvement has been brought about largely by three outstanding contributions.

First, it has been shown how the starved and debilitated patient can be prepared so that he may be operated upon with relative safety.

Second, the widespread preparation of blood plasma both by manufacturing chemists and by hospital laboratories and the improved methods of blood matching for transfusions have made such supportive measures more generally available and safer for use during the operation.

Third, the development of the closed or aseptic type of resection.

MORTALITY

Peritonitis, pneumonia, operative shock are the main causes of mortality following gastric resection. Pneumonia and shock can be almost completely controlled by adequate preoperative preparation of the patient and by proper supportive measures during operation. The work of Whipple, Ravdin, and more recently of Varco, has made us protein conscious. They have shown us that the starved and debilitated patient can be put into improved condition by the use of a high protein, high carbohydrate, low fat diet given either orally or by continuous drip through a nasogastric tube. This diet should be supplemented when necessary by intravenous glucose, amino acids, plasma or blood. Often 1, 2, or 3 weeks are necessary to accomplish this—the length of time depending upon the amount of weight lost by the patient. With this preparation, these patients, if supported during operation by intravenous plasma, are able to stand a long 3 to 4 hour procedure without blood pressure fluctuations and without developing shock.

Where there is no shock, there is rarely pneumonia. Other measures such as guarding against inspiration of stomach contents into the lungs during operation, postoperative suction of mucus from the trachea, high Trendelenburg position after operation, and care in the administration of fluids to the aged patient are important factors in the prevention of pneumonia. The postoperative encouragement of deep breathing, the practice of forceful coughing, the elimination of tight adhesive strapping and caution in the postoperative use of morphine which abolishes the cough reflex are measures which prevent the occurrence of atelectasis and so also cut down the incidence of pneumonia.

PERITONITIS, THE GREATEST DANGER OF RESECTION

The prevention of peritonitis has been a challenge to surgeons since the beginning of gastric surgery. The percentage of deaths from peritonitis following resection for carcinoma of the stomach has been so great that it stands out vividly on the records of modern surgery. Little progress has been made in this fight until the advent of the aseptic closed resection.

The general mortality following resection of stomach for carcinoma has been all too high. According to Livingston and Pack this runs up to 50 per cent with an average of about 23 per cent. Few realize what a large percentage of these deaths is due to peritonitis. Walters, Priestley and Gray (19) in their book *Carcinoma and Other Malignant Diseases of the Stomach* report that at the Mayo Clinic between the years of 1908–1938, 2,772 resections for carcinoma of the stomach were done. They report a general mortality of 16.2 per cent. Of the 450 deaths in this series, 368 were au-

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topsied. Forty-two and two tenths per cent of those on whom postmortem examinations were made, peritonitis was given as a cause of death, pneumonia, 31.3 per cent. At the Mayo Clinic in the 5 year period between the years 1938–1942 inclusive, Gray states that of 596 resections for carcinoma 61 deaths occurred—a mortality of 10.2 per cent. Of these 61 deaths, 28, or 45.8 per cent, died of peritonitis, and 29.6 per cent died from pneumonia. Friedrich and Weber reported 207 resections for carcinoma of the stomach from the surgical clinic at the University in Vienna. They showed a general mortality of 25.1 per cent. In 71 per cent of these cases, peritonitis was given as a cause of death. Parsons and Welch, reporting a series of 100 resections for carcinoma of the stomach at Massachusetts General Hospital, had a general mortality of 35 per cent between the years 1922 and 1936. Their report shows that 33⅓ per cent were due to peritonitis, and another 33⅓ per cent were due to pneumonia. Boyce reported 91 resections for carcinoma at Charity Hospital, New Orleans, with a general mortality of 56 per cent. Of these deaths, 31.3 per cent were due to peritonitis. In our own experience at Veterans Hospital in Minneapolis, in a group of 193 patients admitted for carcinoma of the stomach, we explored 90 and resected 36 by the open method. We had 6 deaths, a mortality of 16.6 per cent. Of the 6 who died, 3 or 50 per cent, died of peritonitis.

This high incidence of peritonitis is understandable when we find that studies made by Seley and Colp show that 93 per cent of cultures taken from patients with carcinoma of the stomach are positive.

Following resection for ulcer, peritonitis has never been greatly feared; nevertheless when we look into the mortality reports, we find that it actually is of considerable moment. Allen and Welch, reporting 151 resections for duodenal ulcer at Massachusetts General Hospital, had a mortality of 9.2 per cent. Four out of 14 deaths, or 28.6 per cent, were due to peritonitis. Hinton, of New York, in reporting a series of 102 resections for ulcer, had 5 deaths. Four of these 5, or 80 per cent, were due to peritonitis. Walters (18), reporting on surgery of the stomach and duodenum at the Mayo Clinic for 1941, in 215 resections for duodenal ulcer, gave 6 deaths. Four of these, or 66⅔ per cent, were due to peritonitis. In our experience at the Veterans Hospital in Minneapolis we have done 100 gastric resections for ulcer by the open method. In this series we have had 8 deaths, a mortality of 8 per cent. One of these, or 12½ per cent, died of peritonitis. What percentage of peritonitis in these statistics is due to contamination at the time of surgery and what is due to postoperative leakage from suture lines cannot be determined. Seley and Colp have shown that 83 per cent of gastric ulcers and 36.6 per cent of duodenal ulcers show positive cultures of the stomach contents.

These figures I am sure will convince the most skeptical that patients with resections frequently die of peritonitis. The extremely high mortality from peritonitis that has followed resection for carcinoma of the stomach has convinced me that the surgeon using the usual open method is not giving his patient all the protection he is entitled to.

PROTECTION AGAINST PERITONITIS

In our fight against peritonitis we now have available the aseptic or closed method of gastric resection. This method has been in use a comparatively short time and indications are that it is likely to do much toward eliminating this dread complication. Wangensteen (22) has done approximately 150 aseptic resections for carcinoma and 400 resections for ulcer. Following resection for carcinoma he has had 1 death from peritonitis. This was a patient in whom a sponge was left at time of operation. Following resections for ulcer he has had 2 deaths from peritonitis. One of these was due to a leak from a suture line and the other to a subdiaphragmatic abscess. Holman (10) reports 65 aseptic resections for ulcer and carcinoma with 1 death from peritonitis. Babcock reported 35 aseptic resections with no peritonitis. We have done 55 aseptic gastric resections for carcinoma and ulcer with no deaths from peritonitis. While this series is comparatively small, it would appear that further reports will indicate we have indeed a powerful weapon against the greatest danger of gastric resection. Since postoperative leak-

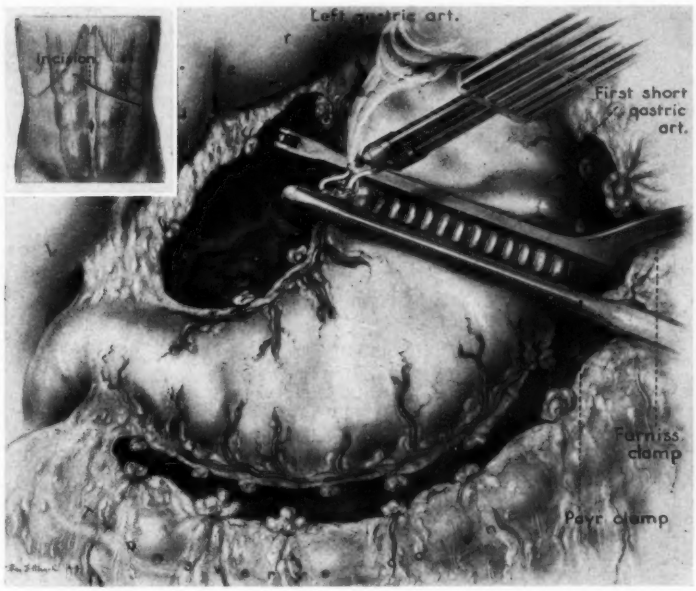


Fig. 1. Furniss and Payr clamps are applied obliquely across stomach and section with actual cautery is started. A cuff of stomach is always left beyond Furniss clamp.

age from the duodenal stump and from the suture lines of the anastomosis is the other common cause of peritonitis, the aseptic technique must include a safe closure of the duodenal stump and a careful application of sutures of anastomosis, augmented by an indwelling nasal suction catheter in both the proximal jejunal loop as well as in the stomach, to take the pressure off both of these points.

ASEPTIC GASTRIC RESECTION

Aseptic resection as applied to the stomach was described in 1940 by Wangensteen (21). He has modified his operation since his original description, and is now doing for ulcer a high resection, removing approximately 75 per cent of the stomach and joining the cut end of the stomach to the side of the jejunum at the ligament of Treitz by a Hofmeister no-loop retrocolic anastomosis. Since his original description there have been articles by Holman (9) and Babcock describing aseptic techniques. We began using the aseptic technique in gastric resection about 2½ years ago, at first limiting its use to carcinoma of the stomach when the indications for the aseptic resection are absolute. As our confidence in the method gained, we began using it in resection for ulcer also. One has only to do a few aseptic resections before being impressed with the smooth postoperative convalescence that these patients exhibit, the minimum of postoperative febrile reaction, and the low incidence of other complications exhibited by these patients. From our own satisfactory experience with the closed resection, I am convinced that this method will be generally adopted. Any technique that holds forth the prospect of eliminating or cutting to a minimum the complication that accounts for 30 to 70 per cent of the deaths following resection for carcinoma of the stomach must be given full and serious consideration by every surgeon.

The technique which I am about to describe is new in the respect that there has been no description of the application of the Furniss clamp to gastric surgery. This clamp as described by Furniss in 1934 has been limited to use in closure of the duodenal stump and to

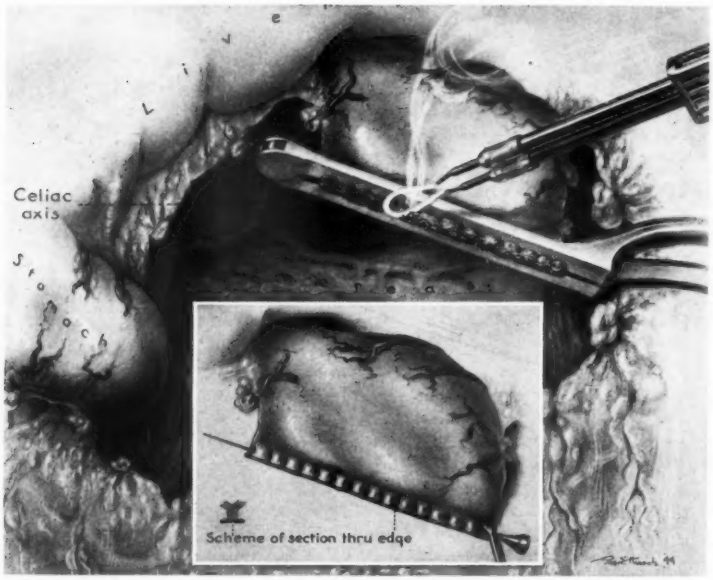


Fig. 2. Mucosa of cuff is first scraped out. The remnant is then thoroughly seared with actual cautery until it assumes a leathery appearance. Inset shows needle pushed through serrated edge and clamp is then removed.

aseptic surgery of the bowel. We became interested in it because it appeared to give a better control of hemorrhage than any other means previously used. With it one can cauterize individually with coagulating diathermy any artery that has not already been controlled by the electric actual cautery and the crushing effect of the clamp itself. With this technique, the clamp is removed prior to inversion of the cauterized edges into the stomach cavity. With the clamp off and the needle having been thrust through the serrated edges to maintain closure of the cut-off viscus, inspection of the cut edges of the stomach and bowel is made possible. Any bleeding artery can then be coagulated with diathermy point or, if one desires, can be ligated. In our experience bleeders occur frequently in spite of thorough electrocauterization.

The method lives up to the three cardinal points of an aseptic technique—thorough crushing of stomach wall, the production of a narrow margin of inverted edge, and adequate control of hemorrhage.

In selecting a clamp for performing an aseptic anastomosis, one must consider two points. First, the crushing surface must not be too wide, for the tissue that is crushed must be inverted into the lumen of bowel. Too much inverted cuff at the angles of the anastomosis is a common cause of obstruction of the distal outlet. The second point is that the clamp should be strong enough to crush tissues forcibly. This is helpful in hemostasis. The serrated crushing surface of the Furniss clamp is approximately 0.5 centimeter wide. There is a screw fulcrum at the end of the handle to cause forcible pressure. Down the face of each blade is a groove approximately one-half the pitch of the teeth. This groove forms a channel through which a long needle may be thrust when the jaws are approximated. This maintains closure of the viscus after the clamp is removed.

ANTERIOR OR POSTERIOR ANASTOMOSIS?

Throughout the literature of gastric resection the argument frequently arises—should

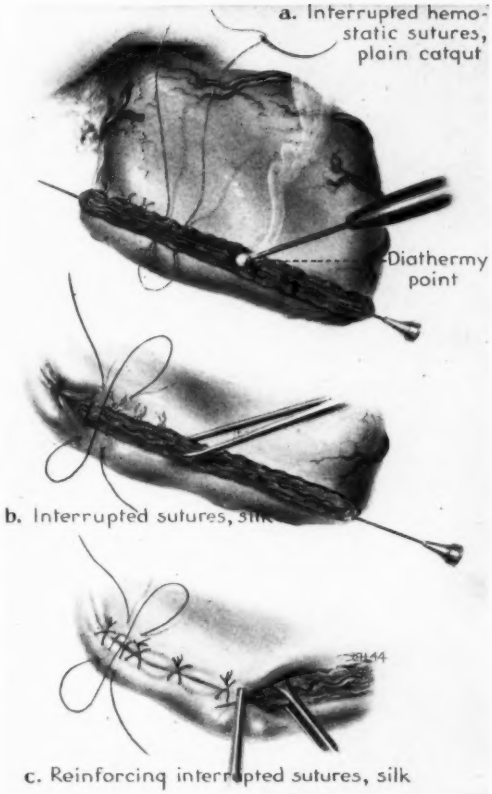

a. Interrupted hemostatic sutures, plain catgut
Diathermy point
b. Interrupted sutures, silk
c. Reinforcing interrupted sutures, silk

Fig. 3. a, Interrupted plain mattress sutures aid hemostasis in Hofmeister portion. Diathermy point coagulates a bleeder. b, Closure of Hofmeister portion is begun, interrupted double Lembert silk sutures being used. c, Furniss needle is pulled down to site of anastomosis and Hofmeister closure is then reinforced with many more silk sutures.

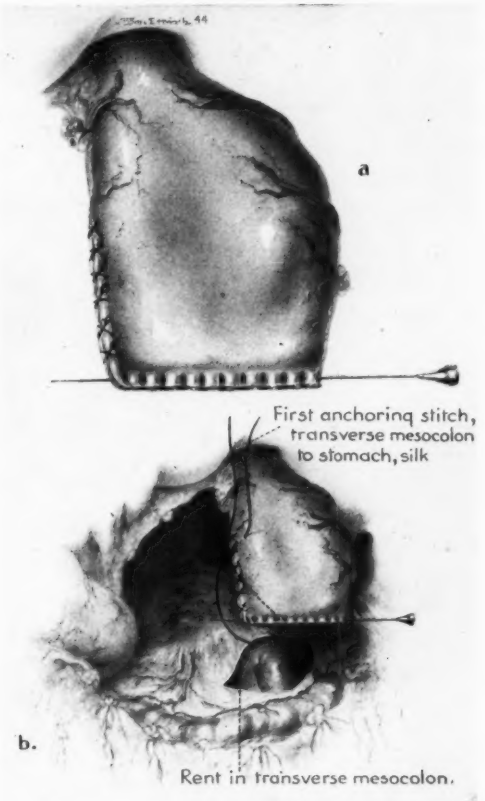


Fig. 4. a, Hofmeister portion has been thoroughly closed with single row of silk sutures and stomach is ready for anastomosis to jejunum. b, First anchoring stitch joining stomach to transverse mesocolon is now conveniently placed. When tied later it will accomplish a rotation of lesser curvature to posterior aspect of rent in mesocolon.

one make the anastomosis posterior or anterior to the colon. Both methods have their staunch and ardent supporters.

We have done posterior anastomoses for some time, and for good reasons. We feel that a quick emptying stomach is an essential of a good gastric resection. Fast emptying means quick discharge of acid from the stomach and in ulcer this is what is desired. I am convinced that a well made posterior anastomosis functions better than an anterior—especially the no-loop anterior as recommended by Lord Moynihan, which approximates the distal loop to the lesser curvature. He had two obstructions in anterior anastomosis when he was doing the reverse method and attaching the proximal loop to the lesser curvature. We had a similar experience with 2 cases in anterior anastomosis in which we attached the proximal loop to the lesser curvature. These patients both developed obstruction of the proximal loop about 3 weeks after operation, necessitating reoperation. One recovered and one died of gangrene of the proximal jejunal loop and duodenum.

I am convinced that the reason many surgeons are having trouble with posterior anastomoses is because they are still using the

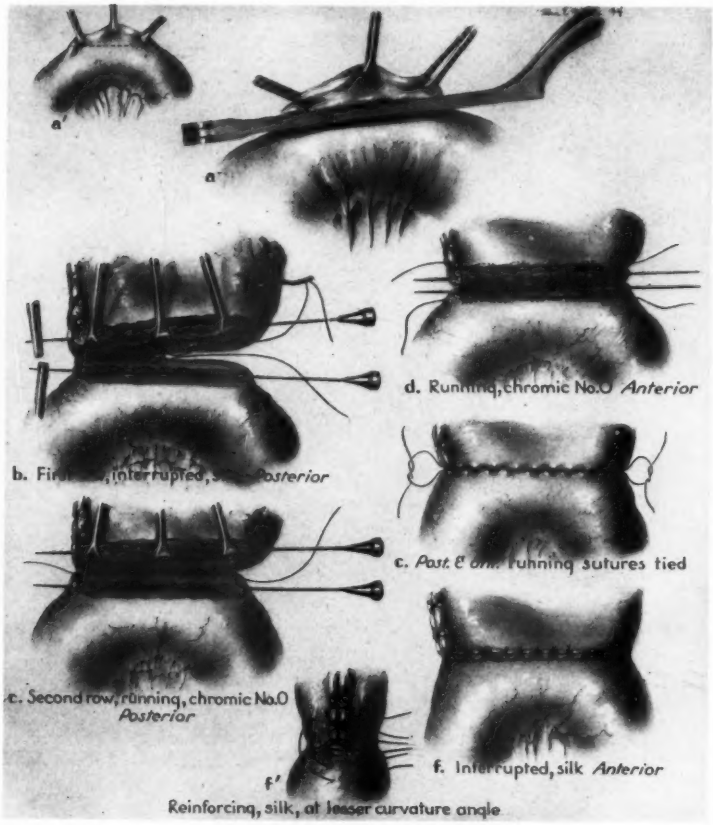


Fig. 5. a, á, Furniss clamp is placed on side of jejunum and a triangular bite is removed with actual cautery. b to f, Steps in suturing of anastomosis. Note that posterior row of silk sutures are so placed as to bring knots on the outside of anastomosis. f', Angle at lesser curvature is carefully protected with three interrupted silk sutures.

Pólya type of anastomosis. When this is done, especially in high resection, the process of bringing the anastomosis comfortably and safely below the attachment of the mesocolon onto the stomach, is very often difficult and hazardous. If, on the other hand, one uses the Hofmeister technique, the placement of the anastomosis well below the mesocolon, so that this cannot impinge upon, or interfere with, the functioning of the stoma, is usually a simple matter. The Hofmeister technique transforms a short, stubby stomach into a long, thin, tubular one, thus making a posterior anastomosis easy.

With the occasional difficult case in an obese person, or in an unusually high resection, one should give some thought to the place where he makes the opening in the mesocolon. With the Hofmeister technique, this opening need not be large—not over 2 to 2.5 inches in diameter. If one makes it posteriorly near the pancreas in the difficult case, he is making it hard for himself. For then he has only the length of the stomach to utilize in getting it below the mesocolon. On the other hand if he makes the opening anteriorly near the colon, he has the width of mesocolon between the opening and the pancreas which

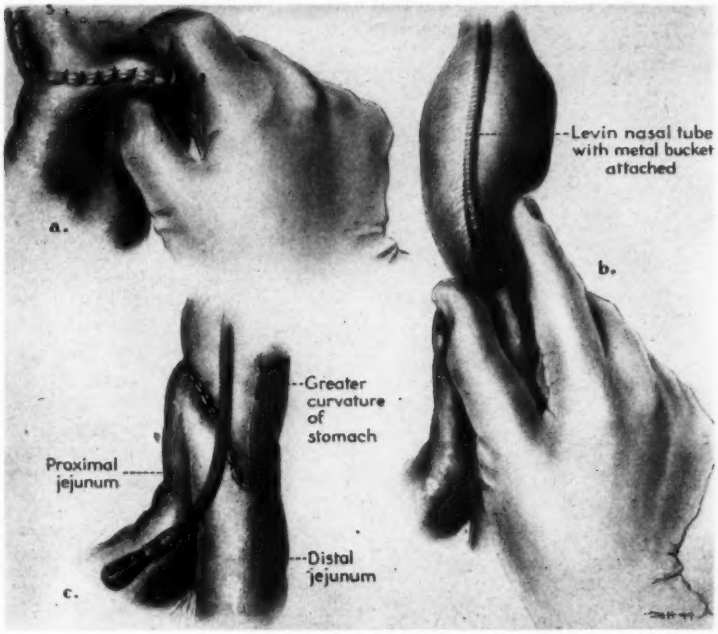


Fig. 6. a, Anastomosis is broken down particularly at inlet and outlet. b and c, Levin tube with metal bucket attached is grasped through wall of stomach and passed through anastomosis into proximal loop of jejunum.

structure is movable and available for making the attachment onto the stomach easier.

Moreover, we feel that in the extremely high resection in a fat person in whom there is difficulty in getting the anastomosis below the mesocolon even when the Hofmeister technique is used, we would rather allow the two loops of bowel to run freely through the slit in the mesocolon and to attach the edge of this to the loops of bowel, doing this in such a way as to separate the loops, one from the other. We prefer this to doing an anterior anastomosis.

There are other reasons why we are committed to a posterior anastomosis. In the first place it allows for making the anastomosis close to the duodenal-jejunal junction. The jejunum is largest at this point which makes for better stoma with less danger of puckering and obstruction of the outlets. Moreover, Wangensteen (23), reminding us of our physiology, calls our attention to the fact that the best hormonal stimulus for elaboration of pancreatic juice is secretin, acting on the pancreas through the blood stream. Secretin is elaborated in the duodenal mucosa by contact stimulation of hydrochloric acid. Therefore, in resection for ulcer, an anastomosis made near the duodenum allows hydrochloric acid to bathe the duodenal wall, thus stimulating the formation of pancreatic juice, which in turn will produce neutralization of the acid (Fig. 10).

Experimentally it seems to have been shown that the farther down the bowel an anastomosis is made, the less resistant the mucosa is to hydrochloric acid. This now appears to be borne out clinically. Kiefer, reporting 173 gastric resections for duodenal ulcer done at the Lahey Clinic, at the recent meeting of the American Medical Association, reviewed 20 cases that subsequently developed gastrojejunal ulcer, or hemorrhages. Sixteen of these operations were done by the anterior

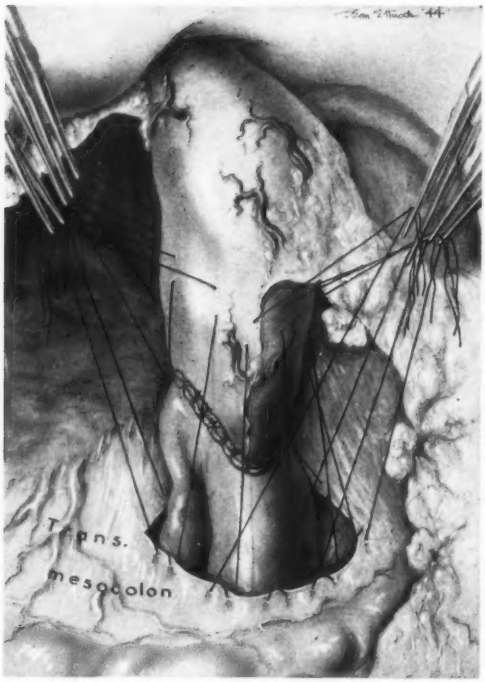


Fig. 7. Remainder of silk anchoring sutures are now placed. These are tied from above after anastomosis has been pulled through rent in mesocolon. These are so placed as to accomplish rotation of stomach, thus making lesser curvature posterior and greater curvature anterior.

method, which means an anastomosis well down on the jejunum. Three resections in which a posterior anastomosis was used, were all by the Finsterer exclusion method, leaving the antrum of the stomach. Whenever this has been done there usually is a high incidence of gastrojejunal ulcer. In 1 case it was not stated whether operation was anterior or posterior. Wangensteen (22), on the other hand, using the posterior no-loop, or short loop anastomosis, has reported approximately 350 carefully followed resections without a single gastrojejunal ulcer. As both Kiefer and Wangensteen report using high resections, it would seem that the outstanding difference between the two series is the use of the anterior, long loop anastomosis on the one hand, and the posterior, short, or no-loop method on the other.

MECHANICS OF A SATISFACTORY POSTERIOR ANASTOMOSIS

I would like here to discuss briefly the mechanics of what I consider a satisfactory, well functioning posterior anastomosis applicable to either the open or the closed method.

The first essential is the use of the Hofmeister procedure. This is basic in the production of an easy, comfortable posterior anastomosis, and there is nothing that will do more toward the elimination of kinks and tension. The next point to consider is the relative size of the openings in the stomach and jejunum. In this respect we are careful to make the opening in the jejunum somewhat smaller than the opening in the end of the stomach. This is accomplished by putting the side of the jejunum on a stretch prior to application of clamp. Then, if we apply the clamp so that the apparent lengths of the openings are the same, the actual opening in the jejunum will be somewhat smaller than the opening of the stomach. This obviates the possibility of puckering that occasionally occurs at the outlets when the converse happens, and the opening in the jejunum is made larger than the end of the stomach.

There is another point that is important in placing the clamp on the jejunum. Instead of taking a straight tangential bite off the edge of the bowel, one should take a triangular bite, wider in its central portion than at its edges. When these two things are done, namely stretching the bowel prior to setting the clamp and taking a triangular bite off the jejunum, when the anastomosis is made, we accomplish a pantaloon effect on the two limbs of the jejunum. This makes for a more vertical mode of entry and exit, and as a result better functioning of the stoma.

THE PREVENTION OF KINKING OF PROXIMAL LOOP AT INLET OF ANASTOMOSIS

The next thing to consider is the length of jejunal loop to be used in a posterior anastomosis, and the optimal direction of the gastrojejunal anastomosis. We have been using a short loop anastomosis, making it about 2 to 3 inches from the ligament of Treitz—allowing only enough room to perform an end-to-end anastomosis in the event of the formation of a

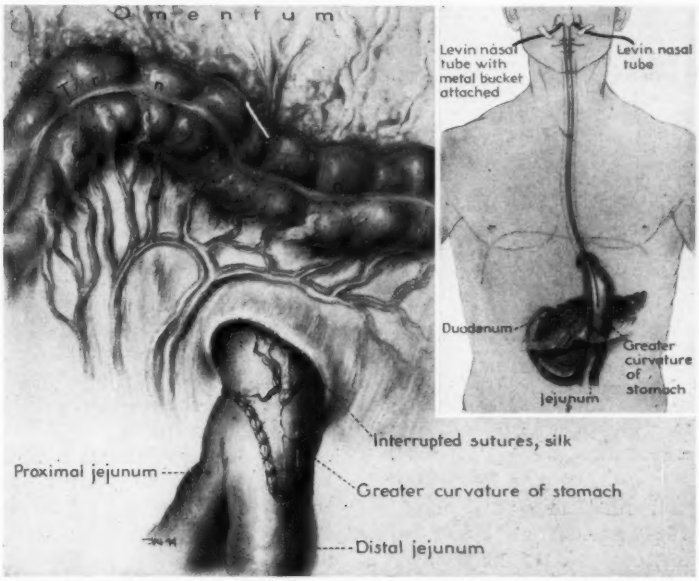


Fig. 8. Anastomosis is brought below mesocolon and sutures are tied from above. These are placed as high above line of anastomosis as possible. Inset shows second nasal tube passed into stomach on patient's return to room.

gastrojejunal ulcer at a future date. This short loop allows hydrochloric acid from the stomach to bathe the duodenal mucosa, and thus stimulate the formation of secretin (Fig. 10). In order to accomplish a safe, short-loop anastomosis, one should anchor the end of the stomach so that it will be held in such a direction as to make possible a comfortable, no kink stoma. To do this we utilize the attachments of the rent in the mesocolon onto the wall of the stomach to control the direction of the stomach as it joins onto the jejunum. Obviously our gastrojejunostomy in a posterior type of resection would be less prone to become kinked, if the lesser and greater curvatures of the stomach, instead of lying in a transverse direction as they normally do, were to lie in a sagittal direction with the lesser curvature posterior, and the greater curvature anterior. If that were the case, the cut end of the stomach would apply itself comfortably to the jejunum, allowing this bowel to lie in a more natural direction as it comes forward from the ligament of Treitz. When this is not done, and the stomach is left to lie in its customary transverse direction, it is necessary for the jejunum to turn over first to the right and then, at its junction with the lesser curvature end of the stomach, make a sharp turn back to the left. No harm is done by rotation of the stomach, but much damage may be done if the jejunum becomes kinked.

This optimum direction of the stomach can be brought about by judicious placement of stitches when suturing the edge of the opening in the mesocolon to the stomach. To accomplish this, the first stitch joining the stomach to the mesocolon approximates the lesser curvature of the stomach to a point in the slit in the mesocolon directly above the place where the jejunum emerges from the ligament of Treitz, or even slightly to the left of this point. A silk suture is used for this purpose (Fig. 4, b). What this does is to rotate the lesser curvature posteriorly, and to the left. The greater curvature conversely rotates anteriorly and to the right. Several more silk sutures are placed about the margin of the slit strengthening the first stitch and maintaining the desired anteroposterior direction of the

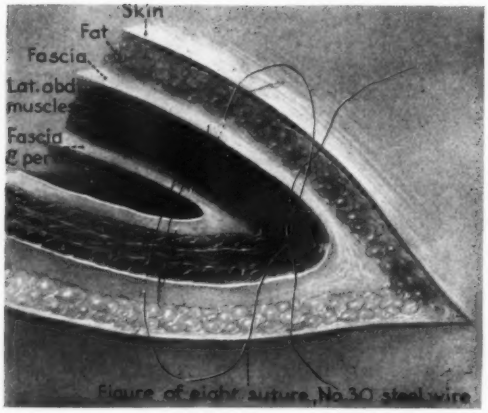


Fig. 9. Abdominal wall is closed with interrupted figure-of-eight No. 30 steel wire sutures.

greater and lesser curvatures at a point directly above the ligament of Treitz. The attachment of mesocolon onto the stomach is made as far above the anastomosis as is possible.

THE "DUMPING" STOMACH

These improvements in the mechanics of a posterior anastomosis—the pantaloon effect produced in the loops of jejunum, the rotation of the stomach so that it lies in a sagittal or anteroposterior plane instead of its normal coronal or frontal plane and held there by sutures to the opening in the mesocolon, the attachment of the mesocolon to the stomach high above the line of anastomosis—all tend to promote a free, well functioning stoma and a quick emptying stomach. This is desirable in any resection but is particularly important in patients with ulcer. There any stasis of gastric secretion is bad. The quicker it is discharged from the stomach and neutralized by alkaline juices, the better. While much has been written about the "dumping" stomach, this is not a particularly objectionable thing. It is true that these patients may complain of some distress following the too rapid ingestion of fluids. However, if they are cautioned to avoid drinking too much fluid with their meals and to eat six times a day instead of three for the first few months following surgery, they usually get along very well. The small bowel tends to adjust itself rapidly to the new conditions and after a time these patients have little distress.

METHOD OF PASSING LEVIN NASAL TUBE INTO PROXIMAL LOOP WITHOUT BREAKING ASEPTIC TECHNIQUE

Preliminary to placing patient on the operating table, a nasogastric tube is passed into the stomach. An ordinary No. 14 Levin tube is used. To the end of this is attached a metal bucket—one that we have taken off of a double lumen Abbott-Rawson tube. The use of this particular type of bucket has been advantageous because of the fact that this bucket gradually widens toward the distal end, a feature which facilitates palpation and allows one to grasp and manipulate it through the stomach wall easier than one could the usual olive-shaped bucket as is used for example on the Rehfuss tube. This tube serves a dual purpose. Suction on it keeps the stomach in an empty, collapsed state during operation—a most important consideration in doing an aseptic resection, and, second, the bucket on the end can be palpated through the wall of the stomach so that at the completion of the anastomosis the tube can be milked down through the stoma into the proximal loop. The duodenum and jejunum are thus kept collapsed during the postoperative period. McClure and Fallis, in 74 resections, had 4 deaths. Three of these were due to obstruction of the proximal loop with subsequent perforation. These probably would not have occurred if a suction tube had been used in the proximal jejunum to decompress this loop of bowel. There should be no duodenal blow-outs if pressure is eliminated from this viscus.

Tying a metallic bucket on the end of the tube makes it possible to place it in the proximal loop without the necessity of opening the anastomosis and thus breaking the aseptic technique. In passing the tube before patient is placed on the table, the blunt tip is first cut off. The tube is fed through the nose, grasped with a forceps as it comes into the throat, and pulled out through the mouth. The bucket is then tied into the tip with silk and the tube swallowed easily. If the metal bucket is already fastened to the nasal tube, a small

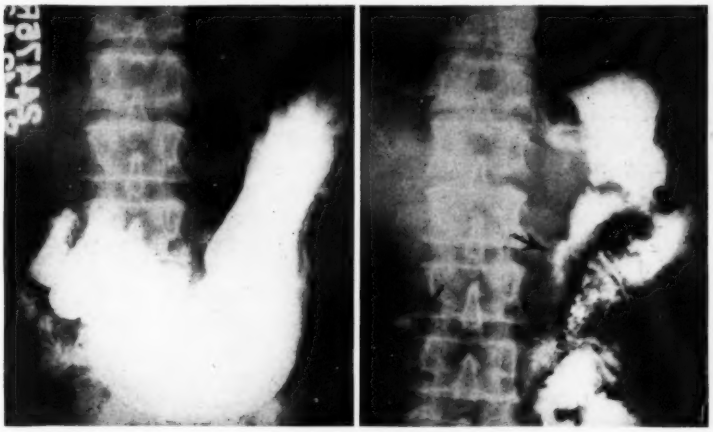


Fig. 10. Roentgenograms taken of stomach before and after resection for ulcer. Picture on right taken immediately after ingestion of barium shows a fast emptying stoma. Arrow points to barium that has gone into proximal duodenojejunal loop. This shows that with a posterior short loop anastomosis hydrochloric acid can bathe the duodenal wall and thus stimulate the formation of secretin.

catheter may be passed through the nose, pulled out through the mouth and tied into the open end of the nasal tube. The nasal tube is then pulled back through the nose in a retrograde manner and the bucket can then be swallowed easily.

There are two methods of keeping both the proximal jejunal loop and the stomach collapsed during the convalescent period. One can use a single nine hole Levin tube and attach the metallic bucket to that. This has sufficient holes to keep both the jejunum and stomach collapsed provided the tube does not become obstructed. We have felt so strongly regarding the necessity of keeping the pressure off both of these organs that we have not been content with using a single tube. Too often a single tube becomes blocked by a plug of mucus that cannot be washed out. Therefore we have been using two nasal tubes, each a No. 14 Levin tube of the usual three hole variety. The first has the metallic bucket attached and is placed through the stoma into the proximal jejunal loop during this operation. The second terminates in the stomach and is inserted either before the patient is taken into the operating room or on return to his room (Fig. 8, insert). These tubes are attached to separate suction bottles. After bile starts to come from the tube terminating in the stomach, one can be fairly certain that the inlet of the stoma is functioning. Soon after that occurs the tube in the jejunum can usually be removed with safety. Patients seem to tolerate two nasal tubes almost as comfortably as one.

ANESTHESIA

For anesthesia we have used spinal almost routinely. This allows the use of cautery and diathermy in the operating room without danger. For the last year we have been using continuous spinal as recommended by Lemmon. We have found that intravenous morphine in small doses has been a helpful adjunct to this. This method has been a great aid in carrying the gastric case through a long operation. During the years that we have used the one dose spinal anesthetic we tried in turn novocain, metycaine and pontocaine reinforced with novocain splanchnic block. None of these has been completely satisfactory. With all of them there is an initial let-down often with a distressing drop in blood pressure. There is also the feeling on the surgeon's part that he must hurry to get through before the anesthesia wears off. With continuous spinal the initial blood pressure drop is usually

minimal, and the subsequent small additional doses allow one to take as much time as is necessary for good surgery.

The anesthetic of choice for gastric resection at the University of Minnesota Hospitals now is cyclopropane given by the closed method and supplemented by curare for relaxation.

THE OPERATION

For more than 2 years we have used the oblique, left subcostal incision transecting the rectus muscle. This incision affords a splendid exposure of the stomach and duodenum and closes readily. We almost routinely make our anastomosis between the stomach and jejunum before closing the duodenal stump. We began doing this when we were using the one dose spinal anesthesia and wished to do this part of the operation while the relaxation was at its height. Moreover, if for any reason a hurried termination of the operation were necessary, we believed that it was best to have this most essential phase of the operation completed. After we had used this method a few times we found that it was easier to mobilize the duodenum after having the stomach transected, free, and under control.

In resection for carcinoma all possible gland bearing gastrohepatic and gastrocolic mesentery should be taken with the specimen. The lesser curvature is mobilized well up toward the esophagus, and the left gastric artery is tied doubly with chromic catgut or heavy silk. The greater curvature is liberated up to the short gastric arteries. One or more of these may be tied, care being taken to leave enough blood supply to maintain the circulation of the stomach which may now be entirely dependent on this source. The stomach wall should be completely denuded of mesentery and fat for about ¾ inch above the line where the Furniss clamp is to be placed. Intervening fat and alveolar tissues interfere with strong union between stomach and bowel.

The Furniss clamp, with handles curved upward, is then applied obliquely across the stomach. It is screwed tightly into place crushing the stomach wall firmly. A Payr clamp is applied about ¼ inch distal to the Furniss clamp, and the stomach is cut across with the electrocautery knife (Fig. 1).

CAUTERIZATION OF CUFF AND HEMOSTASIS

A short cuff of stomach wall is always left to protrude beyond the Furniss clamp. This is an important point in hemostasis as emphasized by Gerbode. The first step in the cauterization of this cuff consists in scraping out the mucous membrane portion. This reduces the volume of the cuff to be inverted. The remainder is then thoroughly cooked with the actual cautery (Fig. 2). As we depend on this chiefly to control bleeding, we spend considerable time in thoroughly searing it. When complete, the cuff presents a cooked, leathery appearance. The cautery is applied only to the cuff and *must not touch the clamp*. If that is done, very little heat is transmitted through the clamp to the wall of the stomach. At the greater curvature end, the volume of cuff is reduced to a minimum in order to cut down on the amount to be inverted at this point which is to be the outlet of the stoma.

The long Furniss needle is now pushed through the clamp sealing off the cut, serrated end of the stomach. The clamp is removed and we depend on the needle to maintain closure (Fig. 2, insert). The protruding end of the needle should be cleansed with an antiseptic. With the clamp off, any bleeders that the cautery has not controlled will soon bleed. These are then coagulated individually with the coagulating diathermy point (Fig. 3, a). This feature of the Furniss clamp which allows for its removal prior to the inversion of the cauterized edges gives one considerable assurance as to hemostasis.

At this point, as an additional aid in the control of bleeding, four or five through-and-through sutures of plain catgut are placed at close intervals along the upper or Hofmeister portion of the anastomosis. These sutures are put in just under the Furniss needle (Fig. 3, a).

THE HOFMEISTER PART OF TECHNIQUE

It was only after numerous trials of different methods that we were able to accomplish a satisfactory Hofmeister technique using the Furniss clamp and needle. This problem was finally solved by the simple expedient of partial pulling out of the needle as described in the following.

After placement of the hemostatic sutures, the closure of the upper part, or Hofmeister portion of the stomach is begun. This is started high on the lesser curvature burying the needle and the cauterized edges of stomach into the wall by interrupted double Lembert sutures (Fig. 3, b). The Furniss needle is easily depressed toward the gastric lumen and the edges of the stomach wall to be sutured readily roll into opposition. These at first are placed not too close together—about ½ inch apart. These sutures are continued until all of the cauterized edge of the stomach is covered except that portion that is to be used for the anastomosis—a length of about 6 centimeters.

The needle is then extracted down as far as this point, still maintaining the site of anastomosis sealed with the needle (Fig. 3, c). Lest there be any leakage, an Allis forceps is applied just above the point of emergence of the needle, so that this portion is kept closed until the anastomosis is completed. Any possible contamination of the needle is taken care of by wiping it off with mercressin, or similar antiseptic. Two Allis forceps are then put on the cut end of the stomach and the viscus is pulled down firmly. With the needle out of the portion closed by the Hofmeister method, and having used interrupted sutures, this procedure will bring about considerable lengthening of the remnant of stomach. After the lengthening process is completed, the Hofmeister portion of the anastomosis is reinforced with several more interrupted silk stitches placed between the original sutures, thoroughly sealing off this area (Fig. 3, c). These stitches take a good bite of serosa and muscularis. A single row of double Lembert silk sutures closely applied is deemed sufficient to seal this portion (Fig. 4, a).

THE ANASTOMOSIS

An avascular area is selected to the left of the midline just above the ligament of Treitz, and a small opening is made. At this point the first silk suture is placed that will later join the lesser curvature of the stomach to the posterior aspect of the slit in the mesocolon. This suture is merely placed at this time and not tied (Fig. 4, b). It is much easier to put it in now than later after the anastomosis is completed. Care must be taken to place this stitch high in the lesser curvature so that the attachment of mesocolon to the stomach will be well above the line of anastomosis. The jejunum is next brought up through the slit in the mesocolon. An Allis forceps is placed at a point about 2 to 3 inches below the ligament of Treitz, marking the proximal end of the anastomosis. A second Allis forceps is placed about 5 centimeters below this point, marking the distal end of the anastomosis. A third Allis clamp is placed between the two (Fig. 5, a′). One must be careful to place all three of these in the midamesenteric portion of the jejunum. The outer two Allis forceps are then stretched apart. The central Allis forceps is elevated so that when the Furniss clamp is applied and the Furniss needle inserted, its central portion will transect the jejunum at about the junction of the inner two-thirds and outer one-third of the bowel, thus removing a triangular wedge from the side of the jejunum. This is removed with electric cautery, again leaving a narrow cuff that is thoroughly seared (Fig. 5, a).

The anastomosis is made by joining the proximal jejunum to the lesser curvature, and the distal loop to the greater curvature side of the stomach. The pointed ends of the two Furniss needles are steadied by a small Kocher forceps. We never use the protecting caps that are supplied with the Furniss needles as there is danger of these slipping off and getting lost. An Allis forceps grasps the stomach and jejunum at the greater curvature end to facilitate handling during suturing (Fig. 5, b).

The anastomosis is accomplished by two rows of sutures—an outer layer of interrupted silk double Lembert sutures and an inner layer of running chromic No. 0 suture. The outer layer of interrupted sutures is started at the lesser curvature going toward the greater curvature end. These are placed fairly close to the needles allowing only room for the inner row of running chromic suture that is to be placed between outer silk sutures and the area crushed by the clamp. The row of interrupted silk double Lembert sutures are inserted in such a way that the knots will be on the outside of the anastomosis when it is completed (Fig. 5, b). When this row is fin-

ished the inner line of running chromic suture is placed. This starts at the greater curvature. These are placed loosely until the entire row is placed. The two ends of running suture are then pulled taut thus bringing the opposing surfaces into snug apposition. The ends of this suture are left loose (Fig. 5, c).

A similar running chromic suture is then placed on the anterior aspect of needles, also at first placed loosely (Fig. 5, d). After both rows are in the four ends are pulled taut. The Furniss needles are now pulled out entirely. The ends of the posterior row of chromic catgut are then tied to the ends of the anterior row of chromic suture, thus completing one row about the anastomosis (Fig. 5, e). A row of interrupted double Lembert silk sutures on the anterior surface completes the anastomosis (Fig. 5, f).

The junction between the proximal loop and the lesser curvature must be protected. This is done by attaching the proximal loop over the lower end of the Hofmeister portion with three or four silk sutures. In placing these sutures, a bite is taken first in the anterior surface of the stomach, next on the posterior surface, and finally a broad bite is taken in the surface of the proximal jejunum. When these are tied, the angle is safeguarded (Fig. 5, f').

The stoma is now broken down with the thumb and forefinger. Care must be taken that this be done particularly well at the inlet and outlet of the stoma where obstructions are liable to occur (Fig. 6, a). Then the bucket attached to the nasal tube is palpated through the wall of the stomach and is milked past the stoma into the proximal loop for a distance of 4 to 5 inches (Fig. 6, b and 6, c). The anesthetist can help at this point by pushing in the nasal tube. We consider this a most essential safety measure in the prevention of tension in this loop of bowel. A twist or kink at the inlet of the anastomosis may form a closed loop of obstructed bowel with resultant gangrene or blowout of the duodenum.

Sutures joining the edge of the slit in the mesentery to the wall of the stomach are best put in before the anastomosis is pulled through this opening. We have already placed the first stitch joining the lesser curvature to the posterior aspect of the slit. The remainder are now inserted, placing them in such a way as will bring about a rotation of the stomach, lesser curvature posterior, and greater curvature anterior (Fig. 7). These sutures, when tied after the anastomosis is pulled through the opening in the mesocolon, will hold the stomach in an anteroposterior direction—the optimal direction for good function and the prevention of jejunal kinks (Fig. 8).

CLOSURE OF DUODENAL STUMP

In the closure of the duodenal stump one cannot be too careful. We usually use the Furniss clamp or Clute's modification. The stomach and portion of duodenum are removed with cautery, the needle inserted, and clamp removed. A running chromic suture is used to invert the end of the duodenum. As this is pulled taut, the needle is removed. This suture is tied to itself at each end. A second row of double Lembert silk sutures reinforces the first layer. The stump is next buried into the wall of the pancreas with several silk sutures taken in the capsule of the gland. It is then covered with omentum.

When it is not technically possible to remove the pylorus and duodenal ulcer, the lower end of the antrum of the stomach is left. When this is done, the antrum mucosa must be removed, otherwise there is a high incidence of gastrojejunal ulcer following resection. This can readily be done by the method of Wangensteen (24). In this technique after dissecting out and closing the mucosal lining without breaking the aseptic technique, the mainstay of the procedure lies in a careful approximation of the submucosal and circular muscle layers of the prepyloric antrum by one or two rows of interrupted Halsted mattress sutures of fine silk. After placing these sutures, the remnants of the antral pouch are cut away leaving only enough tissue to permit easy approximation of the edges *without inversion.*

RESULTS

We have used the Furniss clamp in 46 gastric resections for ulcer. In this series we have had 1 death, a mortality of 2.2 per cent. This death was due to a transfusion or sulfanilamide reaction. This patient became jaun-

diced and died of anuria. We have used this technique in 11 resections for carcinoma. Here also we have had 1 death, a mortality of 9.9 per cent. This was in a poor risk patient with mitral stenosis. He died of cardiac failure in the fourth postoperative day.

SUMMARY

Peritonitis is the most common cause of death following resection of the stomach for ulcer and especially following resection for carcinoma when the open type of anastomosis is used. During the past 5 years published reports indicate that the aseptic or closed method of gastric resection will do much toward the elimination of peritonitis as a complication.

A method of aseptic gastric resection utilizing the Furniss clamp and needle is described. They lend themselves particularly well to the performance of the Hofmeister type of anastomosis.

A means of improving the mechanics of the posterior type of anastomosis is outlined wherein a rotation of the stomach is brought about so as to prevent obstruction of the proximal loop as it joins the lesser curvature of the stomach.

A method of obtaining a pantaloon effect on the afferent and efferent loops of jejunum is described. In this way better function of the stoma is accomplished.

Details of passing a nasogastric suction tube through the anastomosis into the proximal jejunal loop without breaking the aseptic technique are presented.

As it is possible to remove the Furniss clamp before the cut edges of the stomach and bowel are inverted in toward the lumen of the stoma, this method provides a better control of hemorrhage than any other type of closed gastric resection. Because of that feature any bleeders not controlled by the crushing effect of the clamp and the electrocautery may be coagulated individually by diathermy point or ligated.

REFERENCES

1. Allen and Welch. Ann. Surg., 1942, 115: 530.
2. Babcock, W. Wayne. Surg. Gyn. Obst., 1942, 75: 485.
3. Boyce, F. F. J. Am. M. Ass., 1941, 117: 1670.
4. Friedrich and Weber. Arch. klin. chir., 1942, 171: 673.
5. Furniss, H. D. Am. J. Surg., 1934, 23: 379.
6. Gray. Personal communication.
7. Gerbode. Surg. Gyn. Obst., 1942, 74: 468–474.
8. Hinton, J. William. J. Am. M. Ass., 1942, 120: 816.
9. Holman, E. Surg. Gyn. Obst., 1942, 74: 146.
10. Idem. Personal communication.
11. Kiefer, E. D. J. Am. M. Ass., 1942, 120: 819.
12. Lemmon and Paschal. Surg. Gyn. Obst., 1942, 74: 948.
13. McClure and Fallis. Surgery, 1940, 8: 575.
14. Livingston and Pack. Treatment of Cancer and Other Allied Diseases. New York: P. B. Hoeber Inc., 1940
15. Moynihan. Abdominal Operations. Vol. I: 398. Philadelphia: W. B. Saunders Company, 1926.
16. Parsons and Welch. Surgery, 1940, 6: 327.
17. Seley and Colp. Surgery, 1941, 10: 369.
18. Walters, W. Proc. Mayo Clin., 1942, 17: 420.
19. Walters, Priestley and Gray. Carcinoma and Other Malignant Diseases of the Stomach. Philadelphia: W. B. Saunders Co., 1942.
20. Varco. Staff Meeting Bulletin, Hospitals of U. of Minn. Vol. 15, No. 12, January 14, 1944.
21. Wangensteen, O. H. Surg. Gyn. Obst., 1940, 70: 59.
22. Idem. Personal communication.
23. Idem. Proceedings of the Inter-State Postgraduate Medical Assembly of North America, Oct. 1942.
24. Idem. Surgery, 1942, 12: 731.

A COMBINED OPERATION FOR VARICOCELE AND INGUINAL HERNIA

A Preliminary Report

CARL T. JAVERT, M.D., Major, M.C., A.U.S., New York, New York, and
RANDOLPH L. CLARK, M.D., Major, M.C., A.U.S., Jackson, Mississippi

VARICOCELE is a vexing problem to military surgeons. Certain patients are treated conservatively with hygienic measures and a suspensory, and others are operated upon. The reason for using either type of therapy is often ambiguous. Irrespective of the form of treatment used, a certain number of patients continue on sick call and complain of pain and discomfort. This is especially the case when the soldier considers himself malassigned. All too often, malingering or interaural psychopathy are suspected when complaints are legitimate.

Many urologists have condemned varicocelectomy because of the unsatisfactory end-results. It is agreed that the old operation through the scrotum for the excision of the pampiniform plexus is undesirable. Yet surgery should not be entirely abandoned in the treatment of properly selected cases. Under such circumstances, *the combined operation*, consisting of ligation of the internal spermatic vein at the internal inguinal ring and a modified type of herniorrhaphy, is the procedure of choice.

CLINICAL PICTURE OF VARICOCELE

A large varicocele is not necessarily symptomatic, whereas, a small one may be associated with much pain and discomfort. Experience has shown that in either instance, pain may be due in part to an indirect inguinal hernia. For example, of 145 patients with varicocele referred for operation (see Table I), 37 or 25 per cent, had an associated hernia. Conversely, of 102 patients operated upon for a left-sided hernia, 14 per cent had a varicocele. Moreover, 10 patients with varicocele and without a clinical hernia, had a hernial sac of varying size at operation, an incidence of 100 per cent. On occasion, a bilateral hernia is present, or a right hernia and a left varicocele.

The hernia is not always evident clinically. The patient is usually examined only in the erect position and the engorged veins either obscure a complete or incomplete sac, or, prevent the sac from filling with fluid or the intestine. Moreover, the attention of the surgeon may be entirely engaged by the obvious varicocele. The diagnosis of hernia in patients with varicocele is facilitated by examining the patients in *both* the erect and supine positions. The supine position permits the veins to empty and, when the patient strains and coughs, the hernia can be demonstrated more readily.

The varicocele is invariably on the left side. The left testicle is usually the same size as the right and is usually very dependent. However, on occasion, it has been found to be smaller in size and actually atrophic. Cognizance of this should be taken before operation in order to evaluate the results. For the size of the varicocele, the terms, large, medium, and small are descriptive.

The occasional patient will present dilated veins on the left side of the scrotum which disappear after ligation of the internal spermatic vein. At the time of operation the abdominal veins appear to be larger than is usual. This evidence of an established collateral venous blood circulation indicates an abnormal blood flow in the primary, or deep, circulation of the testicle.

COLLATERAL VENOUS BLOOD CIRCULATION OF THE TESTICLE

The venous blood circulation of the testicle is composed of a primary or deep system and a secondary or superficial system of veins as shown diagrammatically in Figure 1. The primary venous system consists of the internal spermatic veins originating in the pampiniform plexus, the vein of the ductus deferens, and the external spermatic veins. The latter anastomose with the internal spermatic veins in the spermatic cord. The internal spermatic veins communicate with the ductus deferens vein in the epididymis and the substance of the testicle.

The secondary venous system is made up of the superficial and deep epigastric veins, the superficial internal circumflex, and the scrotal tributaries of the superficial and deep external pudendal and the internal pudendal veins. The superficial veins of the secondary system communicate with each other and connect with the

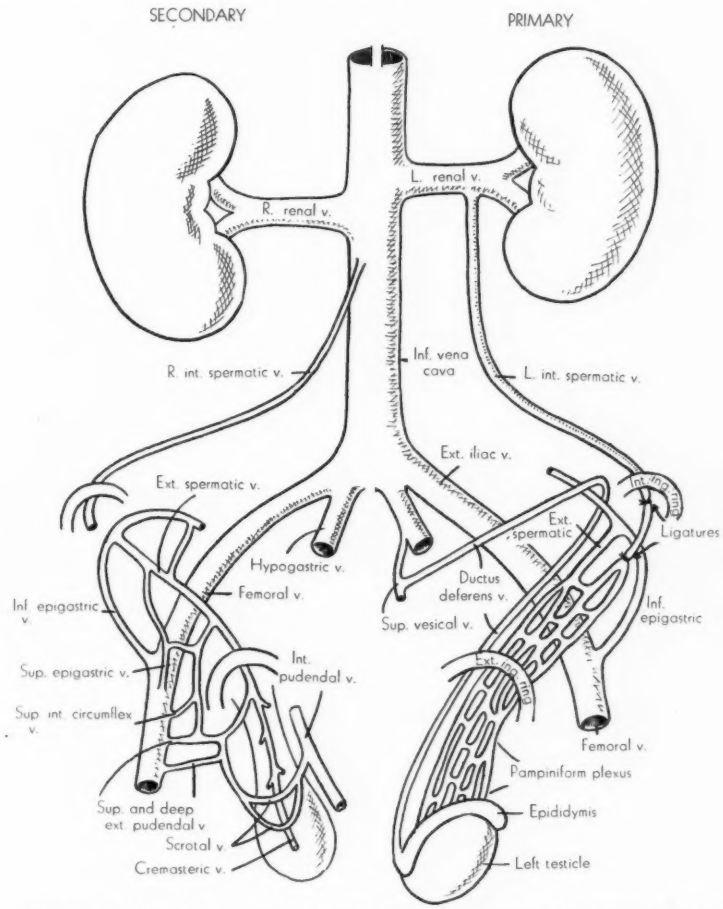


Fig. 1. Diagram of the primary or deep and secondary or superficial systems of veins that provide for collateral venous circulation of the testicle when the left internal spermatic vein is ligated at the internal inguinal ring.

external spermatic veins of the primary system through its cremasteric branches at the external inguinal ring.

The pampiniform plexus consists of numerous convoluted veins which coalesce and become reduced in number in their course upward, and they emerge into the canal as internal spermatic veins. Near the internal ring, the internal spermatic veins usually become one vein although sometimes two are present, while in the retroperitoneal space, there is almost always only one, which empties at right angles into the renal vein. This mode of insertion, with the absence of valves, is usually considered the cause for varicocele.

A retrograde filling of the internal spermatic veins has been observed at the time of herniorrhaphy on patients with varicocele. For example, when the distal portion of the internal spermatic veins are occluded with the gloved thumb and forefinger and the veins are stripped toward the internal ring and then allowed to fill from above, they do so quickly. The retrograde circulation is responsible for the undue distention of the pampiniform plexus known clinically as a varicocele.

The optimum point for ligation of the internal spermatic vein is at its point of termination in the left renal vein, as shown in Figure 1. Ligation at the internal inguinal ring also eliminates the

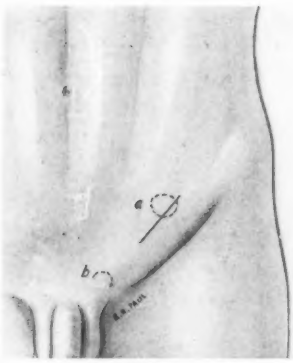


Fig. 2.

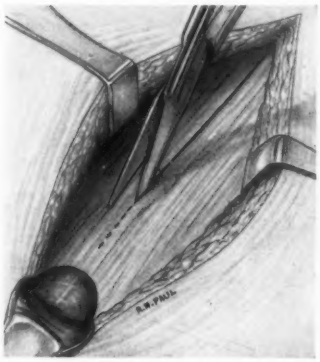


Fig. 3.

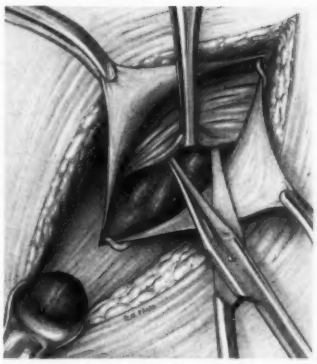


Fig. 4.

Fig. 5.

Fig. 6.

Fig. 7.

Fig. 2. Location and extent of inguinal incision—a, internal ring; b, external ring.

Fig. 3. Incision of external oblique fascia. External ring is not opened ordinarily.

Fig. 4. Dissection of cremasteric muscle from the internal oblique muscle. The cremasteric muscle is also separated from Poupart's ligament (which is not shown in the drawing).

Fig. 5. Longitudinal incision of cremasteric muscle and infundibuliform fascia exposing a dilated internal spermatic vein.

Fig. 6. Internal spermatic vein is doubly ligated above its bifurcation. Vein collapses after proximal ligation. About 5 centimeters of vein is excised.

Fig. 7. Areolar tissue in floor of cord is explored and an indirect, incomplete inguinal, hernial sac is exposed.

static column of blood that is responsible for the varicocele and does not impair the collateral venous circulation either in the cord or at the external ring. Low ligation of the internal spermatic veins near the point of origin in the testicle as in the old operation interferes with the collateral circulation in the pampiniform plexus. It is an improper angiologic procedure and may be compared with ligation of the greater saphenous vein at the ankle for cure of varicose veins.

DISCUSSION OF OPERATIONS FOR VARICOCELE

Ivanissevitch recommends ligation of the spermatic veins in the retroperitoneal space, through a left abdominal incision. Suspension of the testicle with a fascial strip without vein ligation through an inguinal incision is advocated by Londres. Skinner recommends ligation below the external ring and Londres' fascial suspension of testicle. Bertola transplants the internal spermatic veins from the cord to a position beneath the fascia. Bernardi uses an inguinal incision as recommended by Hautz. The external oblique fascia is incised in all of these procedures. None of them correct the associated indirect inguinal hernia, either actual or potential. Failure to do so may be the reason for the persistence of pain even when the varicocele is cured. Since varicocele and

Fig. 8.

Fig. 9.

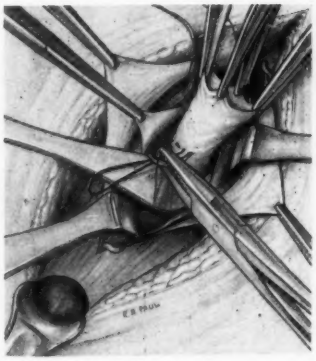


Fig. 10.

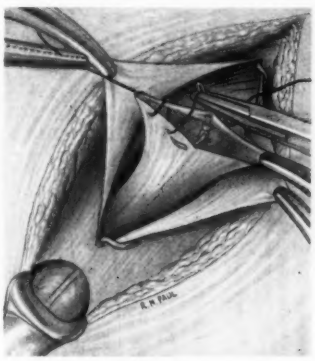


Fig. 11.

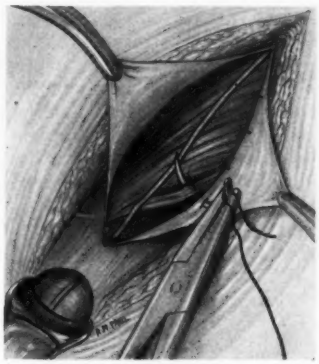


Fig. 12.

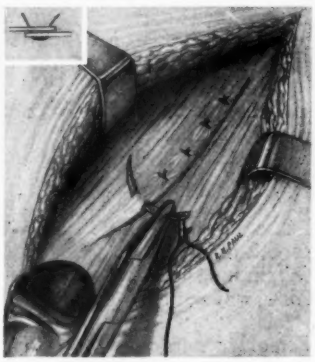


Fig. 13.

Fig. 8. Sac is opened and finger is introduced for investigation of direct inguinal hernia. Note inferior epigastric vessels.

Fig. 9. Prevesical fat is dissected from the sac. Any direct hernia is indirectalized. Sac is also separated from vas deferens, inferior epigastric vessels, and cord structures (not shown).

Fig. 10. Ligation of sac with a continuous mattress suture. Stump retracts high above the level of the conjoined tendon (not shown).

Fig. 11. Transverse closure of cremasteric muscle, incorporating distal stump of the internal spermatic vein. This secures some shortening of the cremasteric muscle and produces some suspension of the testicle.

Fig. 12. Suturing the internal oblique muscle over the cord to the shelving edge of Poupart's ligament. This produces an anatomical relationship of these structures as seen in the female.

Fig. 13. Imbrication closure of the external oblique fascia (see insert).

hernia frequently coexist, an operation for the correction of both is the logical procedure when surgical treatment is decided upon.

The combined operation to be described below comprises internal spermatic vein ligation at the internal inguinal ring, ligation of the hernial sac, muscular suspension of the testicle and herniorrhaphy. Ligation at this point (Fig. 1) does not disturb the anastomosis with the remaining portion of the primary system (ductus deferens and external spermatic), nor does it destroy the communication with the secondary system. An adequate venous collateral circulation is maintained in the epididymis and testicle. Hydrocele has not been observed as a postoperative complication. Likewise, testicular atrophy does not develop because the arterial circulation is not disturbed. Both of these complications are frequent following the old operation through the scrotum. Ligation at the external ring interferes with the collateral circulation to some extent and results are occasionally unsatisfactory, as shown in Table II.

The circumstances leading to the development of the combined operation may be of interest. In the beginning, the old operation was performed on several patients. Dissatisfaction with this pro-

TABLE I.—THE ASSOCIATION OF VARICOCELE AND INDIRECT INGUINAL HERNIA

	Number of cases	Number of hernia demonstrated No.	Percent
Group I (ligation at external ring)	41	0	
Group II (ligation at internal ring, herniorrhaphy)	32	32	
Miscellaneous group	72	5	
Total	145	37	25

TABLE II.—FOLLOWUP (3 TO 15 MONTHS) ON PATIENTS HAVING VARICOCELE OPERATION

	Group I	Group II
Number followed	10	22
Testicle normal	8	22
Testicle atrophied	1	0
Hydrocele	1	0
Testicle not well suspended	2	0
Pain not relieved	6	0
Varicocele still present	2	0
Hernia, inguinal	6	0

cedure led to ligation of the veins at the external inguinal ring, with longitudinal incision of the cremasteric muscle and fascia and transverse closure, in order to suspend the testicle. This type of operation was carried out on 41 patients and they constitute group I, as shown in Tables I and II. Meanwhile, cognizance was taken of the frequent association of varicocele and inguinal hernia. Herniorrhaphy on these patients permitted observation of the static column of blood in the internal spermatic veins causing the varicocele. Finally, ligation of the veins was done at the internal inguinal ring which produced a cure of the varicocele and led to the combined operation. It has been performed in 32 patients and they are found in group II. The remaining 72 patients constitute a miscellaneous group, most of whom were not operated upon because of lack of symptoms, while others with hernia are awaiting operation. Three patients in this group with varicocele had only a herniorrhaphy performed and the varicocele was unrelieved. These were operated upon before ligation at the internal ring was considered a proper procedure. However, their symptoms were relieved.

TECHNIQUE OF THE COMBINED OPERATION

The details in technique in the combined operation are illustrated in Figures 2 to 13. It is performed under intrathecal spinal anesthesia. A left inguinal incision is made and the external oblique fascia is exposed. The inguinal canal is opened to within 2 to 3 centimeters of the external ring and the spermatic cord is separated from the conjoined tendon and Poupart's ligament. It is not otherwise disturbed from its bed in order to avoid unnecessary damage to the collateral circulation. The internal oblique muscle is then retracted upward. A longitudinal incision is made in the anterior portion of the cremasteric muscle and fascia. One large internal spermatic vein and its bifurcating branches are exposed. The other compartments of the cord are not disturbed. The areolar tissue about the internal spermatic vein is dissected with care in order to separate the artery from the vein. The vein is doubly ligated with No. 1 chromic catgut and silk and about 5 centimeters of intervening vein is excised. The proximal ligation is carried out at the internal ring and the end of the vein is allowed to retract upward. The areolar tissue in the medial floor of the cord is explored for the hernial sac which is then mobilized and opened into. With the forefinger within the sac, exploration for direct hernia is performed. Any direct hernia is indirectalized. The prevesical fat is dissected from the sac as is the vas deferens, inferior epigastric vessels, and the cord structures. The sac is ligated with a running mattress suture. After the sac is cut, the stump retracts high above the level of the conjoined tendon. The cremasteric muscle and fascia are then closed transversely so as to secure partial suspension of the testicle. A continuous suture of No. 1 chromic catgut is used for this purpose and the distal end of the vein is included in this suture.

The herniorrhaphy was completed after the technique of Ferguson in the first 20 cases in which the combined operation was done. However, in the last 12 patients on whom the combined operation has been performed, a modified type of herniorrhaphy has been used with good results. The internal oblique muscle is sutured to Poupart's ligament producing an anatomical situation observed in the female. Simple imbrication of the external oblique fascia is carried out. The dissection is less extensive and bed rest and period of hospitalization is shortened in the patients so treated.

POSTOPERATIVE COURSE AND FOLLOW-UP STUDY

The immediate postoperative course in groups I and II has been satisfactory. All patients wore a suspensory for 7 days. Little or no testicular edema has occurred and no thrombosis of the pampiniform plexus has been observed. The patients in group I are allowed up after several days and are back to duty in 10 days. The patients in group II remain in bed for 10 to 16 days depending on the size of the original lesion after which they are allowed up and participate in graduated

Fig. 14, left. Preoperative photograph[1] of patient with a left varicocele and a left indirect inguinal hernia reaching midway into scrotum.

Fig. 15. Postoperative photograph[1] of same patient as in Figure 14. Note inguinal incision, absence of hernia and varicocele, and elevation of testicle.

exercises, and in 16 to 21 days they are discharged to the convalescent program. They are back to full duty in 3 to 6 weeks.

Follow-up on 10 patients in group I indicates that ligation at the external ring is not entirely satisfactory as shown in Table II. For example, hydrocele, testicular atrophy, nonrelief of pain, failure of suspension of testicle and persistence of varicocele, were seen one or more times. The shorter period of convalescence is an advantage mitigated by the poor postoperative results.

The best and most uniform results were observed in group II following the combined operation. Twenty-two of these patients have been observed for a period of 3 months to 15 months. Pain has been relieved in all, and no testicular complications have developed. The left testicles were well suspended at the level of, or higher than, the ones on the right side. The remaining 10 patients on whom the combined operation has been done within the last 3 months show no evidence of testicular disturbance whatsoever. It is logical that such would have occurred if the venous circulation had been rendered inadequate. Figure 14 shows a patient with a varicocele and hernia before operation and Figure 15 shows the same patient after operation. Note the inguinal incision, higher position of testicle, absence of hernia and disappearance of varicocele.

There is no comparison between the excellent postoperative condition of the patient following the combined operation and the old operation through the scrotum. He is free of pain, has no testicular or scrotal swelling or induration, and is cognizant of the well-being of the left testicle. He has had recurrence of neither varicocele nor hernia.

[1]Official Photograph, U. S. Army Air Forces.

SUMMARY

1. The venous circulation of the testicle is composed of a primary or deep system (internal spermatic, originating in the pampiniform plexus; the ductus deferens and external spermatic veins) and a secondary or superficial system (superficial and inferior epigastric, superficial internal circumflex, and the scrotal branches of superficial and deep external pudendal veins and the internal pudendal vein). The external spermatic and its cremasteric branches connect the two systems.

2. The varicocele is due to a distention of the pampiniform plexus by a static column of blood in the internal spermatic vein.

3. Ligation of the internal spermatic vein at the *internal inguinal ring* does not interfere with the collateral venous circulation between the two venous systems through the pampiniform plexus. It eliminates the static column of blood producing the varicocele. This approach also permits correction of the inguinal hernia, if one is present, and permits suspension of the testicle.

4. The old type of varicocelectomy *through the scrotum* for excision of the internal spermatic veins at their point of origin interferes with the collateral circulation between the primary and

secondary systems. This may explain the frequency of hydrocele following this operation.

5. Ligation of the internal spermatic veins at the *external inguinal ring* may also impair the collateral circulation but to a lesser extent. Were it not for this fact, this procedure would be advantageous when the varicocele is uncomplicated by a hernia, because of the shorter period of convalescence.

6. The association of inguinal hernia and varicocele in 14 to 25 per cent of patients referred for operation for hernia or varicocele or both has been observed clinically. At operation all of the 32 patients having the combined operation had a demonstrable hernial sac, an incidence of 100 per cent. The hernia may be the cause of pain in patients with varicocele, and failure to correct it may be the reason for the persistence of discomfort in patients having had the old type of varicocelectomy.

7. The combined operation, as described, is the procedure of choice when a varicocele is associated with an inguinal hernia. It consists of ligation of the internal spermatic veins at the internal inguinal ring, ligation of the hernial sac, muscular suspension of the testicle, and a modified type of herniorrhaphy. Testicular complications have not been observed following this operation.

8. The combined operation may be modified to meet a given situation, i.e., either ligating the internal spermatic vein at the internal inguinal ring *per se*, in the absence of a hernia; or ligating the vein and the hernial sac (if small), and closing in layers.

9. No recurrence of either the varicocele or of the inguinal hernia has been observed following the combined operation.

10. This study is based on a series of 145 cases of varicocele, 41 of which had ligation of the internal spermatic vein at the external ring, 32 had the combined operation, and 72 were not operated upon.

REFERENCES

1. Bernardi, R. Sem. méd., B. Air., 1941, 48: 849.
2. Bertola, V. J. Prensa méd. argent., 1940, No. 32: 1486.
3. Christopher, F. A Textbook of Surgery. 3d ed. Philadelphia: W. B. Saunders Co., 1942.
4. Ferguson. Quoted by Christopher.
5. Ivanissevitch, O. Med. cir. pharm., Rio, 1942, 646.
6. Londres, J. Ann. Surg., 1934, 99: 185.
7. Skinner, H. L. Ann. Surg., 1941, 113: 123.
8. Tonilo, S. Clin. Chir., Milano, 1939, 15: 793.

PRIMARY MASCULINIZING TUMORS OF THE OVARY

JOSEPH A. BURKET, M.D., and IRVIN ABELL, M.D., F.A.C.S., Louisville, Kentucky

OF ALL the neoplastic growths which are to be found in the human body the most interesting are those that function much as any normal organ. This group of neoplasms may affect astoundingly the physiology of the body through the formation of hormones. Included among these tumors are the adenomas of the parathyroid and the islands of Langerhans, and the eosinophilic and the basophilic adenomas of the pituitary.

Several of the best examples of physiologically functioning neoplastic tissue are the feminizing and masculinizing tumors of the ovary. The most common one is the granulosa cell tumor which secretes estrone, resulting in precocious sexual development in young girls, or a return of menstruation in women past the menopause.

There are two masculinizing tumors of the ovary: the arrhenoblastoma and the adrenal cell tumor of the ovary between which it is almost impossible to make a clinical distinction.

The arrhenoblastoma was named by Robert Meyer, the term being derived from the Greek, "arrhenos," meaning male.

After thorough study, Edgar Norris concluded that the term "arrhenoblastoma" should be used only when both the clinical and pathological observations justify its use; that is to say, it is a clinicopathological condition. The term should be reserved for those cases in which there are definite evidences of defeminization and possibly masculinization associated with an ovarian tumor, which microscopically can be so classified. Thus, one is unable to make the diagnosis on the microscopical appearance alone.

Study of the literature reveals this tumor to be quite uncommon. In 1938, Novak (18) reported that there were 45 cases of arrhenoblastoma and added 6 others. Norris, in a critical study excluding cases with no virilism, reduced the number to 29. We have been able to find 20 additional cases. Novak (20), in 1941 estimated that not over 60 acceptable cases had been reported.

The first case of arrhenoblastoma was reported in 1905 by Pick in Germany. This was a tumor containing a cellular arrangement very closely resembling the seminiferous tubules of the testis, and he, therefore, called it a testicular tubular adenoma. In 1915 Bell, in England, made two notable observations: the associated masculinizing changes and also the presence of interstitial lipoid containing elements upon which the degree of masculinization depended. Meyer, in 1915, attempted to classify the pathological pictures of the tumor, dividing them into 3 groups: the *adenoma testiculare*, which is the same as in Pick's original case, and is predominantly tubular; an *atypical group* which appears quite sarcomatous and produces striking masculinizing changes; and an *intermediate group* which is a mixture of typical and atypical tubules as well as solid portions and in which the clinical picture is intermediate between the first two. The first case of arrhenoblastoma in American literature was that reported by Taylor, Wolfermann, and Krock in 1933. However, in 1921, Moots had reported a case of virilism under the title, "Lateral Partial Glandular Hermaphroditism," and this, it is now believed, was an arrhenoblastoma.

The terminology of the adrenal cell tumor of the ovary is very confusing, in part due to the uncertainty of its origin. Cases are reported under a variety of names, among them hypernephroma, adrenal cell rest, and luteoma. Because of this confusion, Rottino has suggested the term "masculinovoblastoma."

The term "hypernephroma of the ovary" was introduced by Peham in Germany in 1899, and possibly we should give him the credit of reporting the first case, except that there was no typical masculinization. In 1908, Bovin reported the first typical case, but even this tumor was probably parovarian in origin.

The adrenal cell tumor of the ovary is quite rare. In 1938, Rottino summarized 7 cases and added 2 more. In 1944, Kepler and associates summarized the histories of 14 cases including one of their own. To these we must add the case reported in 1944 by Greene and Lapp, as well as the 1 reported here, making a total of 16. There are undoubtedly other cases reported under other diagnoses, as was Maxwell's case, which is now classified as an adrenal cell tumor, but was reported as an arrhenoblastoma.

SYMPTOMATOLOGY

The changes which usually take place in a person with a masculinizing tumor may be divided so that there will be first a loss of feminity and later possibly masculinization.

Fig. 1.

Fig. 2.

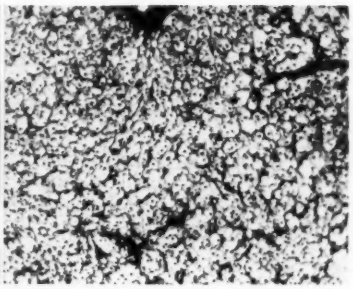


Fig. 3.

Fig. 1. Masculinizing ovarian tumor removed from woman giving a 16 year history of defeminization and masculinization.

Fig. 2. Cross section of tumor.

Fig. 3. Photomicrograph of section of tumor showing typical adrenal cortical cells.

Defeminization. Usually there is first of all a persistent amenorrhea with sterility and then an atrophy of the breasts. The external genitalia are usually normal. There may be an abnormal change in the deposit of fat so that there is a loss of the rounded contour characteristic of the female. The heterosexual libido usually remains unchanged with the exception perhaps of late in the disease.

Masculinization. Hirsutism usually appears rather early and the beard may become quite heavy, even requiring a daily shave. There is masculine distribution of the pubic hair and a recession of the hair line of the head. The skin becomes dark and rough and acne is quite common. There is a lengthening of the vocal cords resulting in a voice of lower register; an "Adam's apple" may result from an overgrowth of the laryngeal cartilages. The clitoris is usually hypertrophied after several years.

If there is a typical picture of defeminization and then masculinization associated with a tumor of the ovary, clinically the working diagnosis should be arrhenoblastoma because of a greater frequency, though one must consider the adrenal cell tumor of the ovary and also bear in mind that in many cases one may find only an ovarian cyst with masculinization resulting from another cause.

It is practically impossible to differentiate the adrenal cell tumor from the arrhenoblastoma. However, masculinization resulting from the arrhenoblastoma is essentially the same as that resulting from excess administration of testosterone; in fact, the changes are thought to be due to the production of testosterone or a similar hormone by the Leydig cells which constitute part of this tumor. On the other hand, as Kepler has pointed out, when the changes result from adrenal cortical hyperplasia or adrenal rest tumors of the ovary, there are definite metabolic disturbances resulting in the so called Cushing syndrome. In these cases of masculinization one usually finds an associated hypertension, polycythemia, and diabetes. The hypertension may be due to overproduction of some compound similar to desoxycorticosterone; the diabetes may be caused by the adrenal diabetogenic hormone; there is no suggestive cause of the polycythemia. In differentiating these tumors Kanter stresses the importance of chemistry studies. If the masculinization results from an adrenal tumor there will be a decrease in the serum sodium and an increase in serum potassium, while the urinary sodium is increased to three times the normal and the potassium is decreased. Also, if the virilism results from adrenal cells, the nitrogenous retention may be five or six times the normal. The sex hormone secreted by the adrenal cells produces sex characteristics of the opposite sex, so that a woman develops amenorrhea, breast atrophy, enlarged clitoris, and hirsutism, while the male has breast hypertrophy, testicular atrophy, female distribution of adipose tissue, and loss of libido.

The masculinizing syndrome may be caused by several conditions and we must differentiate in particular those cases caused by ovarian tumors from the following. An adrenal cortical tumor may be demonstrated by the x-ray after the perirenal injection of air. Cushing's disease or basophilic adenoma of the anterior pituitary gland is a polyglandular condition of pituitary origin with hyperplasia of the adrenal cortices and overactivity of the thyroid gland; there is amenorrhea, loss of scalp hair, hypertrichosis and often hypertension; occasionally the clitoris hypertrophies; an x-ray of the sella turcica would probably show evidence of the tumor.

Surgery is the treatment of choice for both types of tumor. The condition is usually unilateral and so the other ovary should be preserved, particularly in younger women. There have been many examples of pregnancy following the removal of these tumors. However, it must be emphasized here that these tumors are malignant, or at least potentially so, the growth being continuous and progressive, with death resulting from malignant metastases. It is recommended that x-ray be given if there are evidences of metastasis or recurrence; radiation should be given in maximum dosages because less is stimulating.

After removal of the tumor there usually is a return of menstruation within a month. The breasts resume normal size in a comparatively short time. The disappearance of masculinization is much slower, the hirsutism remaining for a very long time; the hypertrophied clitoris may have to be amputated. If there is a recurrence there is again defeminization.

HISTOGENESIS

The origin of these tumors is still unknown but a number of theories have been postulated. Meyer and Novak believe that the arrhenoblastoma arise from embryonic remnants of the seminiferous tubules in the hilus of the ovary, or, as Bauer expresses it: the arrhenoblastoma arises from vestigal male gonadogenic structures. McLester believes that the tumor is teratomatous in origin.

The most likely explanation of the origin of the adrenal cell tumor is that it arises from an adrenal cell rest in the ovary. However, there are those who believe that it has a lutein cell origin.

PATHOLOGY

Arrhenoblastoma. These tumors are unilateral and usually solid, although some may be cystic. There may be degeneration. The size varies considerably, some tumors attaining a diameter of 20 centimeters (6). The color is variable from a yellow to a reddish-blue. The one gross distinguishing feature is the presence of multicentric nodules. The microscopic picture varies considerably with the distribution of the epithelial cells: (1) tubular, (2) cylindroid, (3) diffuse or sarcomatoid. We must also recall the classification of Robert Meyer, as presented earlier in this paper. There are pale staining interstitial cells, as reported by Bell, and the degree of masculinization is dependent upon the presence of such elements.

Microscopically, the malignancy of these tumors is shown by the presence of multiple mitotic figures, variation in size and staining of cells, and large nucleoli. Regardless of the histological appearance, clinically the tumor must be considered at least potentially malignant, having a tendency to invade and to metastasize after years. While the growth is to be considered malignant and should be removed, other pelvic structures should not be disturbed at the time of operation.

Adrenal cell tumor of the ovary. These tumors are also unilateral and vary considerably in size. Saphir and Parker reported one of microscopic size. The one reported in this paper measured 16 by 13 by 8 centimeters. All are solid. A characteristic gross feature is the golden-yellow color. These tumors are usually encapsulated by thinned out ovarian cortex.

Microscopically, the cellular picture is almost identical with that noted in the ordinary hypernephroma: large granular polyhedral cells lie in a mosaic arrangement mainly around numerous, fine capillary vessels. There is very scant fibrous tissue. The sharply demarcated cell walls are quite striking, never being found in the granulosa cell tumor or in a corpus luteum. These large, polyhedral cells contain, as a rule, lipoid material; glycogen has been found in several of these tumors.

All cases thus far reported have been benign except Smith's (25) case which was atypical in certain respects; this patient died after 4 years. Kepler and Dockerty's tumor is histologically malignant. The case to be reported here is both pathologically and clinically malignant.

CASE REPORT

The patient was a 36 year old woman admitted to the hospital April 30, 1942, complaining of an abdominal tumor which was first noticed after dieting and losing 40 pounds of weight during the previous year. On questioning, she revealed that she had not menstruated since the birth of her second child 16 years before. Shortly after the birth of the child hirsutism began to develop, the face and neck became flushed and somewhat bluish, and the voice deepened. The patient was hiccoughing occasionally at the time of admission.

Examination. Blood pressure was 124/78. There was a bluish-red flush of the face, neck, and chest. There was a heavy beard that required daily shaving and a heavy growth of hair elsewhere, with a masculine distribution; the hair of the head was thin, and there was a recession of the hair line. The thyroid gland was not enlarged. There was a small "buffalo hump" in the cervicothoracic region. The abdomen was filled with what was apparently a multinodular tumor, probably arising in the pelvis. On pelvic examination a small uterine tumor was found, apparently separate from the large abdominal tumor. The clitoris was not enlarged.

The red cell count was 4,520,000; the hemoglobin was 84 per cent; and the white cell count, 7,500. The urinalysis was essentially negative.

The clinical diagnoses were: fibromyoma of the uterus and a multiple ovarian tumor, probably arrhenoblastoma.

Operation was performed under spinal anesthesia. The abdomen was opened, and a small amount of free fluid was

noted. The tumor in the lower abdomen was found to arise from the left ovary and to extend into the broad ligament. It was removed. The uterus, approximately four times the normal size, was not disturbed. The right tube and ovary were negative. The tumor mass felt in the upper abdomen consisted of a huge liver containing many nodules, some quite large. The spleen was approximately five to six times normal size. There was no other evidence of metastasis.

After operation the axillary temperature was 102.8 degrees on the 3rd day but was normal the following day and continued so. The patient was troubled considerably with hiccoughing during the entire postoperative course. The pulse was very rapid. On the 7th day she was quite a bit weaker, the eyes and skin were observed to be jaundiced, and this was more pronounced the following day, when she was somewhat moribund. On May 9, 9 days after operation, and the first time in about 16 years, there was vaginal bleeding. The following day she was comotose, and death came the following night, 11 days after the operation. Unfortunately no autopsy permission could be obtained.

Pathology. The pathological studies were by Dr. Harry M. Weeter. The specimen is an ovarian tumor, measuring 16 by 13 by 8 centimeters having a somewhat nodular surface. On sectioning, it shows numerous rounded to irregular areas presenting a variety of colors, some being reddish-gray, others yellow, resembling corpus luteum, and others having a hemorrhagic appearance. There is considerable grayish stroma. The fallopian tube, which is stretched over the tumor, is essentially negative.

Microscopic examination. The tumor is moderately vascular. The outer margin is covered by a thin, fibrous capsule. Two types of cells seem to predominate. The cells of one variety are rounded to hexagonal and seem to be dispersed irregularly through a light stroma with no definite arrangement. The nuclei are small and lie either in the center or to one margin of the cells. The cytoplasm is quite clear and slightly granular. The cells of the second variety lie somewhat in cords. The nuclei are rounded to oval and are moderate in size. The cytoplasm is moderately dense and presents a granular to fatty appearance.

Pathological diagnosis. Masculinizing ovarian tumor of adrenal cortical origin.

Sections of the tumor were examined by Dr. Emil Novak (21) who considers it a malignant adrenal cell tumor originating in the ovary.

SUMMARY

Two masculinizing tumors of the ovary, the arrhenoblastoma and the adrenal cell tumor of the ovary, are discussed. Each is found to be quite uncommon and to produce a similar clinical alteration of physical appearance and sexual function, there first being a defeminization and later masculinization.

Surgery is the treatment of choice for these tumors, and, if there be a recurrence, each tumor being at least potentially malignant, there is again defeminization.

A case is reported of a masculinizing ovarian tumor removed from a patient giving a clinical history of 16 years' duration. At operation numerous metastases were found in the liver and subsequent coma suggested cerebral involvment. Nine days after removal of the tumor, menses began for the first time in 16 years. The patient died on the 11th postoperative day. Autopsy permission was refused. Histologically the tumor was of adrenal cortical cell origin, primary in the ovary.

REFERENCES

1. Baldwin, I. G., and Gafford, J. A. Endocrinology, 1936, 20: 373.
2. Bauer, J. T. Bull. Ayer Clin. Lab., 1939, 3: 259.
3. Bell, W. Blair. Proc. R. Soc. M., 1915, 8: 77.
4. Blackmun, R. L. Am. J. Obst., 1942, 43: 1036.
5. Bovin, E. Nord. med. Ark., 1908, 15: 1.
6. Dockerty, M. B., and MacCarty, W. Surg. Gyn. Obst., 1939, 68: 767.
7. Glynn, E. E. J. Obst. Gyn. Brit. Empire, 1921, 28: 23.
8. Greene, H. J., and Lapp, W. A. Am. J. Obst., 1944, 47: 43.
9. Kanter, A. E., and Klawans, A. H. Am. J. Cancer, 1940, 40: 477.
10. Kepler, E. J., Dockerty, M. B., and Priestly, J. T. Am. J. Obst., 1944, 47: 43.
11. Marchand, F. Virchows Arch., 1883, 92: 14.
12. Maxwell, A. F. West. J. Surg., 1937, 45: 134.
13. McIntyre, W. K. J. Obst. Gyn. Brit. Empire, 1942, 49: 41.
14. McLester, J. B. Arch. Int. M., 1937, 57: 680.
15. Meyer, R. Am. J. Obst., 1931, 22: 697.
16. Moots, C. W. Am. J. Obst., 1921, 1: 864.
17. Norris, E. H. Am. J. Cancer, 1938, 32: 1.
18. Novak, Emil. Am. J. Obst., 1938, 36: 840.
19. Idem. Gynecological and Obstetrical Pathology. Philadelphia: W. B. Saunders, 1940.
20. Idem. J. Am. M. Ass., 1941, 116: 947.
21. Idem. Personal communication.
22. Novak, E., and Long, J. H. J. Am. M. Ass., 1933, 101: 1057.
23. Peham, H. Mschr. Geburtsh. Gyn., 1899, 10: 685.
24. Pick, L. Berl. klin. Wschr., 1905, 17: 502.
25. Rottino, A., and McGrath, F. W. Arch. Int. M., 1939, 63: 686.
26. Saphir, William, and Parker, M. L. J. Am. M. Ass., 1936, 107: 1286.
27. Schattenberg, H. J., and Harris, William. South. M. J., 1939, 32: 734.
28. Schiller, W. Arch. Gyn., Berl., 1933, 156: 513.
29. Ibid., 1935, 160: 344.
30. Taylor, J. M., Wolfermann, S. J., and Krock, F. Surg. Gyn. Obst., 1933, 56: 1040.
31. Van Kirk, F. W., Jr., and Edwards, E. A. Am. J. Cancer, 1939, 37: 209.
32. Young, H., and TeLinde, R. W. Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases. Baltimore: Williams & Wilkins Co., 1937.

SACROCOCCYGEAL SINUS (PILONIDAL SINUS) IN DIRECT CONTINUITY WITH THE CENTRAL CANAL OF THE SPINAL CORD

HENRY A. SHENKIN, M.D., ANDREW D. HUNT, Jr., M.D., and
ROBERT C. HORN, Jr., M.D., Philadelphia, Pennsylvania

THE embryologic origin of sacrococcygeal sinuses has been in dispute since the very time of the description of the entity, itself. This has, in general, been resolved to two opposing theories: (1) that they result from persistence of coccygeal vestiges of the neural canal and (2) that they are the result of invagination of the surface epithelium. The former theory appears to be the most widely held and best supported (6, 7, 10, 12) but the latter has its firm adherents (2, 4, 5, 15).

In support of the first theory, evidence is presented from the study of embryos that the caudal end of the neural canal is early pinched off and an epithelial sac communicating with the skin in the sacrococcygeal area is produced. Just proximal to this, the neural canal seals off and forms the filum terminale. Generally the caudal epithelial sac atrophies and disappears about the 5th intrauterine month. It is the persistence of this sac that forms sacrococcygeal cysts and sinuses, according to the first theory. In confirmation of this supposition are several case reports which describe sacrococcygeal sinuses as being in connection with the dura or even running subdurally as dermoid cysts (1, 9, 14, 16). In a few patients, it has been inferred that sacrococcygeal sinuses communicate with the subarachnoid space because of the presence of a thin, watery discharge from the sinus, regarded as cerebrospinal fluid, or because of the development of meningitis in these cases (11, 13). In none of these latter cases was an autopsy performed, and the exact relationship of the sinus to the central nervous system could not, therefore, be demonstrated. Fox, commenting on such cases, expressed the opinion that a few drops of clear fluid discharged from the sinus could not be accepted unquestionably as being cerebrospinal fluid and that the occurrence of a meningitis associated with a dermal sinus might result merely from a lack of bony protection or from extension by way of the lymphatics or blood stream.

In the case to be reported here, with complete autopsy studies, the relationship of a sacrococcygeal dermal sinus to the central nervous system is demonstrated. We believe, therefore, that the embryological origin of sacrococcygeal sinuses, or pilonidal sinuses, is in relation to persistent sacrococcygeal remnants of the neural canal, rather than primarily due to a faulty development of the surface epithelium.

From the Department of Neurosurgery, the Laboratory of Neurosurgical Pathology, the Department of Pediatrics, and the Laboratory of Surgical Pathology of the University of Pennsylvania.

REPORT OF A CASE

J. K., male child, 22 months of age, was admitted to the Hospital of the University of Pennsylvania with acute urinary retention of 30 hours' duration. There had been no antecedent infection nor were there accompanying symptoms other than progressive irritability incident to the distention. Family and birth histories were of no significance and the child had developed normally, both mentally and physically. At birth, a small "cyst" had been noticed at the base of the spine. X-ray pictures were taken and the mother was informed that the lesion was of no importance. It had been decided that surgical excision was not necessary.

Physical examination revealed a well nourished child in acute distress. The rectal temperature was 101.8 degrees F., the lower abdomen was exceedingly tender, and the bladder was palpable at the umbilicus. The neurologic examination was negative. Over the sacrum, in the midline, was a soft, pink, round mass, about 2 centimeters in diameter, at the inferior margin of which was a minute sinus opening. The mass was not inflamed or tender.

Catheterization yielded 250 cubic centimeters of clear urine. The patient was immediately relieved and began taking fluids well. A retention catheter was left in place. For the next 3 days, he ran a steady fever, of 102 to 104 degrees, which was assumed to be the result of urinary tract infection. He was given sulfamerazine in dosage sufficient to maintain a blood level of 15.9 milligrams per cent. However, he became slowly but steadily worse. He was less active and no longer walked about the crib. On his fourth hospital day, there was questionable nuchal rigidity and a slightly positive Kernig's sign. These symptoms became very pronounced during the next 24 hours and lumbar puncture was performed. A small amount of thick, yellowish-brown, foul-smelling fluid was obtained. The fluid was loaded with polymorphonuclear leucocytes. Flow was too slow to obtain a pressure reading, and the amount obtained was insufficient to make possible a protein determination. Culture revealed microaerophilic, nonhemolytic streptococci, diphtheroids, and gram negative anerobic nonspore forming bacilli of the bacteroides group. On the following

day, examination revealed complete paraplegia and anesthesia of both lower extremities and of the perianal region. Lumbar puncture again revealed thick, foul-smelling, purulent material. Cisternal puncture yielded a cloudy but thin fluid, the culture of which revealed organisms identical with those obtained on lumbar puncture.

The opinion at this time was that the child was suffering from a meningitis and the difference in consistency of the lumbar and cisternal fluids indicated the presence of at least a partially localized abscess in the lumbosacral portion of the intravertebral canal. The rapidly developing transverse myelitis substantiated this. The mixed type of infection, and particularly the presence of an anerobic organism, pointed to an extrinsic source of contamination. The sinus leading from the sacral dimple seemed the most likely avenue for the entrance of the infection. The only other positive finding was a polymorphonuclear leucocytosis ranging from 7,000 to 16,800. Within a few hours after the development of the transverse myelitis, laminectomy was performed.

Operation. The first to the fourth lumbar laminae were removed. The posterior epidural space was clean and, therefore, the dura was opened and cloudy, obviously infected, spinal fluid flowed into the wound. This, however, did not resemble the thick, purulent fluid previously obtained on lumbar puncture. The exposure was such that the lower end of the cord, the conus and the beginning of the cauda equina could be seen. The dorsal surface of the cord was injected in three or four spots. These small areas were about 2 to 3 millimeters in diameter and appeared to be bruises. On retraction of the cord laterally, toward the right, a pocket was found, anterior to the cord, containing free pus and many bits of cheesy and necrotic material. A rubber tissue drain was placed in this pocket and let out through the lower end of the incision. The dura was left wide open, the muscle was brought together with wire, and the subcutaneous tissue and skin were closed with silkworm gut.

The child failed to rally following operation, continuing with high fever (104–105°). He was restless and vomiting and finally passed into coma, dying 56 hours after operation.

Autopsy report. The thoracic and abdominal viscera were grossly and microscopically normal, save for the lungs and the urinary bladder. The former showed passive congestion and the latter, a cystitis. Beneath the wound, over the lumbar vertebrae, there was an area of purulent reaction in the subcutaneous tissue and, beneath this, a purulent cavity where the lumbar spines and laminae had been resected. The dura in this area was partially open and the rubber drain circled, in the subarachnoid space, around the cord to its anterior surface. The cord was completely surrounded by a sticky, greenish white exudate which appeared to be too thick to drain. This exudate was adherent to the cord and to the arachnoid as high as the dissection was carried, which was about the seventh cervical vertebra. The extradural space was entirely free of pus. The lower end of the sacrum had a 6 millimeter hiatus and the skin dimple, over the sacrum, was connected by a fascia-like band, through this hiatus, with the lower portion of the spinal dura. Tension on the skin moved the dura downward. Injection showed the extrasacral portion of this tract to be patent, and radiopaque oil was injected through the skin dimple and demonstrated to be within the spinal canal (Fig. 1). Dissection revealed the conus medullaris to be in direct continuity with a large cystic dilation of the filum terminale which was filled with pus and measured approximately 4 centimeters in length and 2 centimeters in diameter. The long roots of the cauda equina surrounded this pus-containing sac and were themselves heavily covered with a thick, purulent exudate. The dilated, pus-filled filum terminale could be demonstrated to be in direct continuity with the sinus opening into the sacral dimple below, and with the central canal of the spinal cord above (Fig. 2). This sac was, however, partially divided into two compartments, the more caudal compartment containing thicker débris, in clumps. The spinal cord, on multiple transverse section, was seen to be swollen and the seat of numerous, fresh, small hemorrhages, as high as the ninth thoracic segment. The gross architecture of the lumbar portion of the cord was entirely distorted. The brain, which weighed 880 grams, revealed flattening of the cerebral convolutions and the meninges, in the depths of the sulci, contained a slight amount of milky exudate. The basilar surface of the brain was covered with a thick, greenish-white, purulent exudate extending from the medulla rostrally over the inferior surface of the cerebellum, pons and mid-brain and filling the interpeduncular space. The ventricular system showed moderate, symmetrical dilatation, but there was no gross evidence of an ependymitis. The cerebral hemispheres were considerably swollen and there were many petechial hemorrhages, particularly in the cerebral white matter in relation to the lateral ventricles, in the pons, and in the white matter of the cerebellum.

Microscopic examination. The contents of the intravertebral canal from the ninth thoracic vertebra to the sacrum, including the dermal sinus, were sectioned transversely into 1 centimeter blocks, from each of which representative sections were cut and stained. Several of the blocks were cut serially. The dermal sinus was lined with stratified squamous epithelium and contained a small amount of epithelial débris. The subjacent tissues were heavily scarred. The sinus opened directly into the widely dilated sac-like cavity surrounded by the roots of the cauda equina. The caudal portion of this cavity was also lined by stratified squamous epithelium and in its wall were well formed hair follicles and sweat glands (Fig. 3). Its walls also contained many inflammatory cells and engorged small blood vessels. The epithelial lining was destroyed in many places and the lumen contained a thick, purulent exudate in which much débris of epithelial origin could be distinguished. The rostral portion of the cavity was lined by a single layer of low columnar cells (Fig. 4) and could be demonstrated to be continuous with the central canal of the lumbosacral cord. The exudate in the central canal and the rostral portion of the sac communicating with the dermal sinus was purulent but did not contain the epithelial débris present in the lower portion of the tract. The block containing the communication of the two differently lined portions of the dilated and cystic filum terminale were sectioned serially and revealed that these two portions overlapped each other and made a side to side junction (Fig. 5). Externally, there was no break in the structure to indicate the site of this division. Figure 6 shows the microscopic appearance of the junction of the two different types of lining of the cavity.

The spinal cord, as high as the tenth thoracic segment, was the site of a centrally located, partially encapsulated abscess (Fig. 7). The abscess was about the central canal and had destroyed most of the gray matter. About the periphery of the abscess was a moderately heavy glial proliferation which had formed only a partial capsule. No connective tissue had been laid down in the abscess wall. The remaining portions of the cord were edematous, infiltrated with mononuclear cells, and contained proliferated, hypertrophied glial elements. Where the anterior horns were not completely destroyed, the ganglion cells were in all the various stages of necrosis and many had already disappeared.

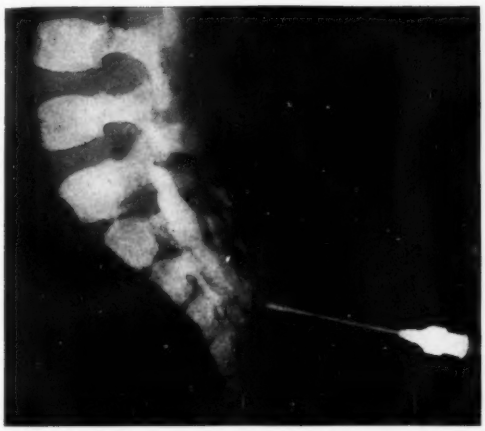


Fig. 1. Roentgenogram of specimen demonstrating continuity of sacrococcygeal sinus with intervertebral canal. Radiopaque oil has been injected through sinus in skin dimple.

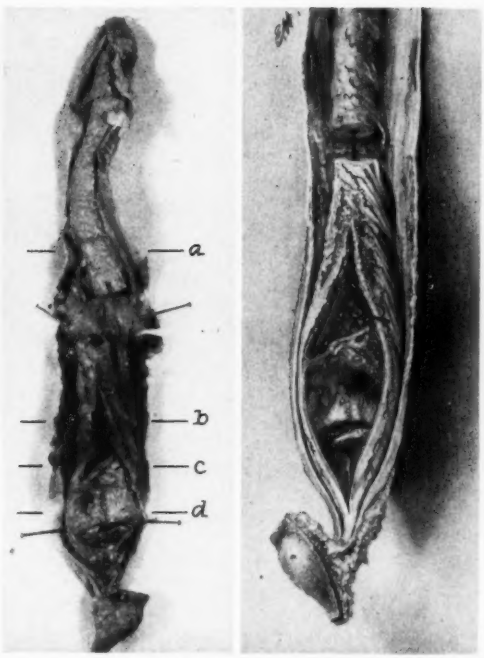


Fig. 2. a, left, Photograph of autopsy specimen. *a*, *b*, *c*, and *d*, are the levels from which photomicrographs (Figures 3, 4, 6, 7) are taken. b, Artist's conception of a, showing in detail the relation of the skin dimple and dermal tract to dilated filum terminale. A probe can be seen passing from rostral portion of filum terminale up through the central canal of the spinal cord.

The subdural and subarachnoid spaces can be considered as a whole, since the arachnoid could not be identified. These spaces were filled with thick, purulent exudate. This exudate, in the lumbosacral region, was composed chiefly of lymphocytes and plasma cells in a network of heavy collagen and precollagenous tissue and newly formed blood vessels. The nerve roots were deeply enmeshed in this organized inflammatory tissue. Immediately beneath the dura, the exudate appeared to be more recent, being composed chiefly of polymorphonuclear leucocytes, with little or no evidence of organization. The dura was intact for the most part but was infiltrated with inflammatory cells. At the operative site, the dura was much thinned and more heavily infected, with an acute, purulent exudate covering its outer as well as its inner surface.

The thoracic meninges were also filled with a thick exudate, but this was composed almost entirely of polymorphonuclear cells with little connective tissue proliferation. The meninges at the base of the brain were filled with a purulent exudate consisting of many polymorphonuclear cells, fewer mononuclear cells, and necrotic débris. An inner layer of this meningeal exudate at the base of the brain appeared to be of longer standing. This consisted chiefly of lymphocytes, plasma cells, and fibroblasts, in a network of fibrin and young connective tissue. The ganglion cells of the brain stem showed both mild and severe toxic changes. The meninges over the convexity of the brain revealed a patchy infiltration of inflammatory cells, most marked in the sulci. This infiltration consisted chiefly of round cells with occasional clumps of polymorphonuclear cells and some necrotic débris in the depth of the sulci. The meninges over the hippocampal gyrus revealed a more acute, necrotizing, suppurative inflammation than was seen over the dorsolateral aspect of the brain. The cortex everywhere appeared edematous and the cells showed toxic changes.

In summary, the anatomic findings in this case demonstrate a dermal sinus, presenting in a sacrococcygeal dimple, to be in direct continuity with a patent and dilated filum terminale which, in turn, is in continuity with the central canal of the spinal cord. This is, therefore, a concrete example of the relationship of sacrococcygeal dermal sinuses with abnormalities in development of the neural canal. It is the failure of obliteration of the coccygeal medullary vestiges, as described by Herrmann and Tourneux and emphasized by Gage, that may give rise to these congenital developmental lesions. This case, indeed, proves the hypothesis which Gage drew from his embryologic studies, viz., that a sacrococcygeal sinus could be in continuity with a persistently patent filum terminale and even the spinal cord.

Walker and Bucy thought that cases of dermal sinuses communicating with the contents of the intravertebral canal at higher levels than the sacrococcygeal region were evidence against the theory of a persistent neural canal as the origin of the histologically similar sacrococcygeal dermal sinuses, in so far as it failed to explain the former situation. Nevertheless, they offer, as an ex-

Fig. 3.

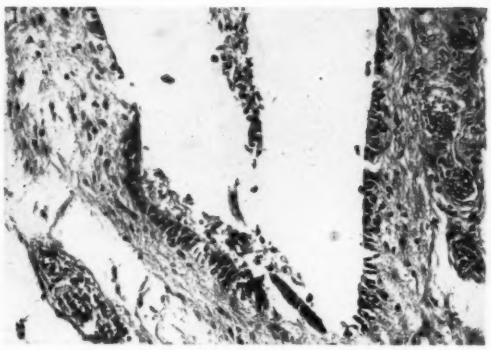
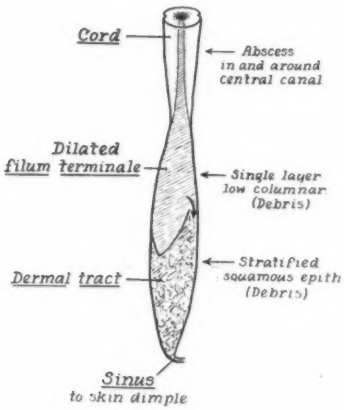


Fig. 4.



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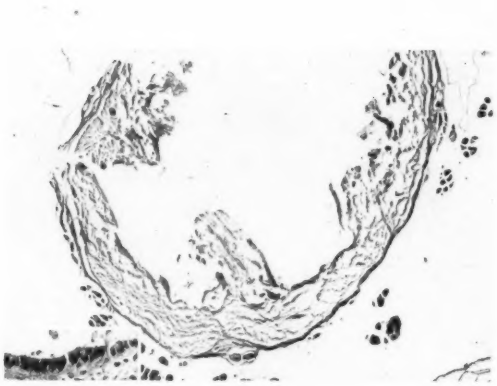

Fig. 6.

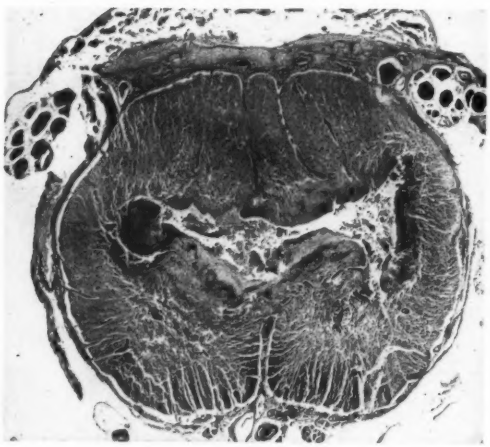

Fig. 7.

Fig. 3. Stratified squamous epithelium lining sac-like dilatation of the dermal sinus. A hair follicle is present in the upper left corner. Section is from level, d, in Figure 2, a (Hematoxylin and eosin, ×70).

Fig. 4. Columnar epithelium lining rostral portion of cavity. Débris is present in the lumen. Section as indicated at, b, in Figure 2, a (hematoxylin and eosin, ×140).

Fig. 5. Diagram of lateral view of specimen illustrating the mode of communication of the dilated filum terminale with the dermal tract.

Fig. 6. Junction of the two differently lined portions of the dilated filum terminale. Section is through level, c, in Figure 2, a (hematoxylin and eosin, ×4). The insert in lower left corner shows the columnar epithelial lining of left portion of cavity (hematoxylin and eosin, ×140). The epithelial lining of the right portion of the cavity, which is in continuity with the skin lined tract, has been destroyed at this level.

Fig. 7. Abscess about central canal of lumbar cord. Level at, a, as indicated in Figure 2, a (hematoxylin and eosin, ×6).

planation for these cases of higher segment dermal sinuses, the theory of imperfect cleavage of cutaneous epithelial ectoderm in the first intrauterine month. Thus, the neural tube carried down with it a narrow invagination of skin. This, they felt, supported the hypothesis of cutaneous ectodermal invagination as the origin of sacrococcygeal dermal sinuses. This is rather confusing until it is realized that the proponents of this latter theory think of the abnormality in development, which leads to pilonidal sinus formation, as lying entirely within the cutaneous ectoderm. Therefore, Walker and Bucy's cases, and even their own hypothesis of origin, support the concept that the abnormality is principally a faulty development of the neural canal. Kooistra, in presenting a case of pilonidal sinus occurring at the level of the third thoracic spine and communicating with the spinal cord, also stated a belief that faulty development of the neural canal is the basis of these congenital lesions. However, failure to demonstrate a connection with the central canal in any reported case is offered as an objection. The case described in this paper meets even this objection.

The meningeal and intramedullary infection producing the clinical picture which brought the patient to our attention traversed the patent pathway from the sacrococcygeal sinus. Spinal cord abscess is rare, usually occurring as a metastatic lesion in general sepsis. This fact, plus the rarity of the malformation present in this case, makes it understandable that the diagnosis was not made earlier in the course of this patient's hospital stay. It was the opinion of the urologist, who performed the catheterization upon this patient, that a congenital urethral band or stricture was the cause of the urinary retention. The pediatricians, who saw the child during the first few days, suggested that the retention might be the first clinical effects of a spina bifida occulta. Spinal cord or meningeal infection was not considered until the appearance of the nuchal rigidity; and the possibility of a localized abscess in the lumbar region was not taken into consideration until after the development of the paraplegia. However, in view of the location of the abscess, it seems unlikely that surgical intervention at any stage of the process could have been entirely successful. Had the sacrococcygeal sinus been removed earlier in the life of this child, it is possible that such a bizarre and tragic termination might have been prevented. This case serves, therefore, to emphasize the recommendation of others (3); namely, that a persistent congenital sinus in the midline of the back should be excised.

SUMMARY AND CONCLUSIONS

1. A case is presented in which a congenital sacrococcygeal dermal sinus was in direct continuity with an abnormally patent and dilated filum terminale and the latter, in turn, with the central canal of the spinal cord.

2. This is offered as evidence that sacrococcygeal sinuses (pilonidal sinuses) originate as a malformation in the development of the neural canal.

3. The development of an intramedullary spinal cord abscess and a purulent meningitis by contamination through the dermal sinus in this case indicates the importance of early excision of such congenital lesions.

REFERENCES

1. BOLDREY, E. B., and ELVIDGE, A. R. Ann. Surg., 1939, 110: 273–284.
2. BOSTROEM, E. Zbl. allg. Path., 1897, 8: 1–98.
3. CRAIG, R. L. Surgery, 1943, 13: 354–367.
4. FÉRÉ, CH. Bull. Soc. Anat. Paris, 1878, 3: 309–312.
5. FOX, S. L. Surg. Gyn. Obst., 1935, 60: 137–149.
6. GAGE, M. Arch. Surg., 1935, 31: 175–189.
7. HERRMANN, G., and TOURNEUX, F. C. rend. Acad. sc., 1887, 104: 1324–1326.
8. KOOISTRA, H. P. Surgery, 1942, 11: 63–74.
9. LIST, C. F. Surg. Gyn. Obst., 1941, 73: 525–538.
10. MALLORY, F. B. Am. J. M. Sc., 1892, 103: 263–277.
11. MOISE, T. S. Surg. Gyn. Obst., 1926, 42: 394–397.
12. OEHLECKER, F. Deut. Zschr. Chir., 1926, 197: 262–279.
13. RIPLEY, W., and THOMPSON, D. C. Am. J. Dis. Child., 1928, 36: 785–788.
14. STAMMERS, F. R. A. Brit. J. Surg., 1938, 26: 266–274.
15. STONE, H. B. Ann. Surg., 1924, 79: 410–414.
16. WALKER, A. E., and BUCY, P. C. Brain, Lond., 1934, 57: 401–421.

THE PATHOLOGY OF EXPERIMENTAL CLOSTRIDIAL INFECTIONS IN DOGS

BENEDICT VICTOR FAVATA, D.V.M., M.D., ANDREW H. DOWDY, M.D., ROBERT L. SEWELL, M.D., and JAMES G. VINCENT, Rochester, New York

IN 1900, Welch published his observations on the morbid conditions caused by gas gangrene organisms. He pointed out that the liver was the seat of early and abundant development of gas. Rabbits killed a few minutes following the intravenous injection of the gas bacilli and kept in a warm place for 6 to 8 hours were found to have a large amount of gas in the blood, organs, and other tissues. This accumulation of gas was thought to be the result of air embolism. Gas was also seen in the lymphatics, mesentery, omentum, and peritoneal cavity. Welch demonstrated that the gas bacillus may multiply in the body without gas formation, and called attention to the fact that the bacilli may be seen in clumps in the spleen and kidney surrounded by necrosis but without gas. He also reported 1 case of meningitis and 1 case of gas gangrene of the brain with cavity formation. Most of the cases which he observed represented gas bacillus growth in the body after death.

Kaufman described a fatal case of gas gangrene in which the heart, spleen, liver, and kidney were swollen, soft, pale, spongy, and honeycombed with innumerable tiny cavities. The myocardium had gas filled spaces. He concluded that the muscles are usually soft, vacuolar, and waxy, with laminated destruction. The muscles showed edema associated with hemolysis, innumerable bacilli, fibrin, and leucocytes. The gases encountered were thought to result from the bacterial action on muscle glycogen. He attributed death to toxemia.

Callander and associates state that gas gangrene is essentially a disease of the muscles. They believe this predilection is principally because of the high glycogen and glutathione content. The disease is manifest within 6 to 48 hours following infection. The muscles swell in the sheaths and the infection travels upward, rarely laterally. There is an absence of inflammatory reaction. The path of the infection (Eliason and associates) follows the muscle bundles. Complete muscle degeneration results from the interruption of the blood supply which is brought about by the excessive swelling.

The gas gangrene bacilli are incapable (Ireland and Coupal) of producing the disease by their presence alone. Failure of circulation, damaged tissue, and a progressive increase of these factors are necessary in order to produce the true clinical picture of the disease. Ireland and Coupal believed that death intervened by respiratory failure rather than by cardiac paralysis.

Pasternack and Bengtson studied the changes produced by the toxin of Clostridium septicum in rabbits, mice, guinea pigs, and pigeons. They concluded that hyaline degeneration was the essential and most important lesion of the heart, and that this was the probable cause of death in gas gangrene. If the animal survived over 4 days, fibroblastic scars of the myocardium were seen. The cardiac ganglia showed no changes. The liver revealed lesions in a small percentage of animals. It was often engorged by red blood cells. They found a nephrotoxic property of the toxin.

Sewell reported a case in which there was gas gangrene of the trunk with recovery and residual cardiac damage.

The route by which the toxin is given is important and has a bearing on the type of damage. Mice and rabbits die by receiving intravenous toxin of Clostridium septicum. When the toxin is given subcutaneously in guinea pigs, it fails to produce death, even when large doses are given. Severe local necrosis may result and the animal usually recovers. This is true when the toxin is given intramuscularly (Bengtson and Robertson).

Clostridium welchii also produces hemolysins for red blood cells of most animals including chickens (Ireland and Coupal).

W. Straub and Lautenschlager, working with "gasoedema" toxin stated that it "had an action like that of digitalis on the isolated frog's heart and that this action was blocked by antitoxin."

In our experimental work on gas gangrene in dogs, we have seen that the diseased muscles have returned to an approximately normal state in dogs which have recovered following treatment. The literature records repeated observations of skele-

From the Department of Surgery and the Department of Radiology, University of Rochester. The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Rochester School of Medicine and Dentistry, Rochester, N. Y.

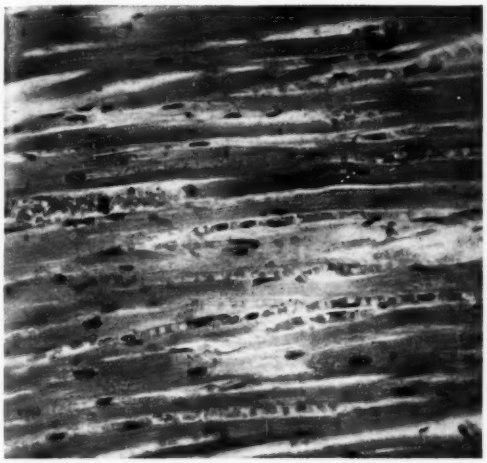

Fig. 1. Heart muscle, ×267, showing relatively severe changes. Dog No. A-126 (Y8571). This dog was a control which had been inoculated with a mixed culture (No. 2) of gas gangrene organisms. The animal succumbed within 12 hours after it had been inoculated. Examination of the heart muscle revealed the presence of swelling, hyalinization, and fragmentation. Pallor of the nuclei is also seen.

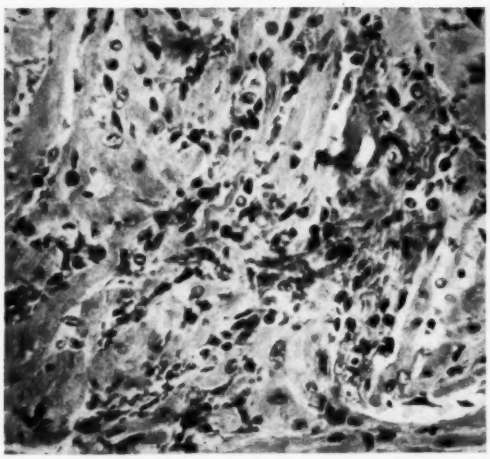

Fig. 2. Heart muscle, ×267, showing organizing necrosis. Dog No. A-135 (Y8710). This dog was inoculated with a mixed culture (No. 2) of gas gangrene organisms. Therapy consisted of sodium sulfadiazine and antitoxin. Dog died 10 days after inoculation. Gastrointestinal tract was filled with bloody fluid and numerous ascarids. Section shows some of muscle fibers swollen with loss of striations and nuclei. Mononuclear cells and fibroblasts present.

tal muscle regeneration in cases of typhoid, pneumonia, injuries, wounds, infections, and invasions by tumors, et cetera. Forbus gives a careful review of the subject of skeletal muscle regeneration. Volkmann believes that undisturbed sarcolemma is an essential requisite for the proper development of the regeneration of the muscle fibers. Experimental regeneration was produced as early as 1892 by Kirby. Olafson has produced experimental regeneration in the skeletal muscle in lambs. In reviewing our microsections he found that the regeneration as seen in his animals compares with that seen in skeletal muscle which has recovered from gas gangrene. Forbus presents evidence that regeneration of experimentally destroyed muscle is apparently total without scar formation.

Experimental: A large number of dogs were used in the study of the therapeusis of gas gangrene. The pathological material was studied in 96 of these dogs. Twenty-six were untreated controls. Forty-three received one or more therapeutic agents.

Healthy adult dogs were inoculated with a mixed clostridial infection. Untreated control dogs were inoculated either with the mixed infection or with the individual clostridial strains. The organisms used were Clostridium welchii, Clostridium septicum, Clostridium novyi, Clostridium sordellii, or a mixture of these four organisms plus Staphylococcus aureus (mixture No. 2). The inoculum, carefully prepared under rigid conditions and standardized as uniformly as possible, was grown in a Douglas heart infusion broth containing chopped beef heart. The method of inoculation was the same as previously described by Dowdy and Sewell.

The definitive agents for therapeusis were sodium sulfadiazine, penicillin, polyvalent gas gangrene antitoxin,[1] or combinations of these agents, administered intravenously. The dosage is indicated for each group studied (see Tables). Sodium sulfadiazine was administered so as to maintain, as closely as possible, a continuous blood level of 15 to 20 milligrams per cent for the periods noted in the charts. The drug content of the blood was checked at frequent intervals. The therapeutic results of the various methods of treatment will be presented in a subsequent paper.

Autopsies were performed on representative animals selected from each experimental group as soon after death as possible. Most of the recovered dogs were killed by intravenous nembutal and chloroform. All of the organs except the brain and spinal cord were examined routinely. The

[1]Lederle's pentivalent

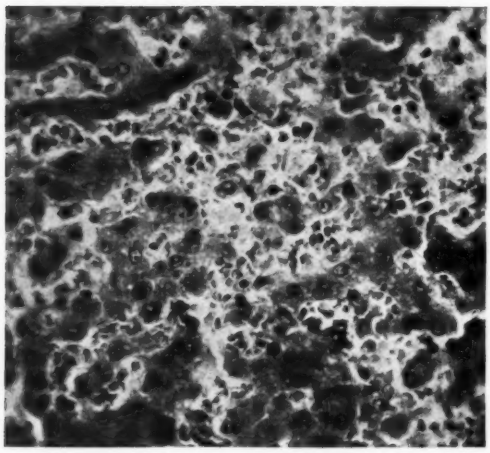

Fig. 3. Liver, ×267, showing focal injury of the liver cells. Dog No. A-106 (Y8547). This control dog was inoculated with a mixed culture (No. 2) of gas gangrene organisms. Death occurred 40 hours after inoculation. This microscopic section reveals marked engorgement of the sinusoids with red blood corpuscles. There is also revealed injury to the cells at the central portions of the lobules.

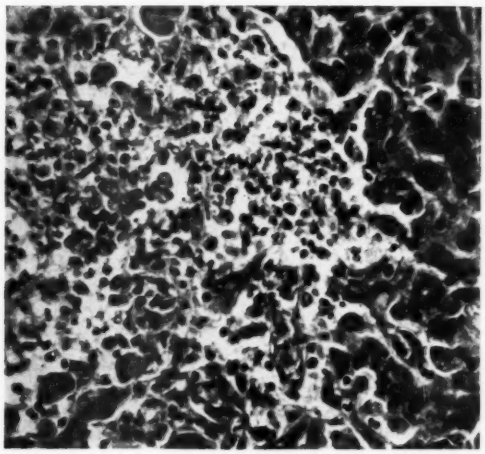

Fig. 4. Liver, ×267, showing an organizing focus of necrosis. Dog No. P-128 (Y8653). This dog was inoculated with a mixed culture (No. 2) of gas gangrene organisms and was treated with sodium sulfadiazine and penicillin. Recovery was satisfactory. The animal was sacrificed 10 days after inoculation. Note the necrosis of liver cells, the acute and chronic inflammatory cells, and the fibroblasts. Interstitial edema is seen in other portions of the liver.

brain and spinal cord were studied with negative results in 4 dogs dying of the infection. The spinal fluid was clear. We did not feel that nerve tissue changes were sufficient in these animals to warrant special staining techniques which are necessary to bring out detailed changes. Nerve bundles studied by ordinary hematoxylin and eosin stains showed no obvious changes even though some were seen in the midst of the area of severe muscle necrosis at the site of inoculation.

The tissues and organs of the body most involved were the inoculated muscles with their surrounding structures, and the heart and the liver. These will be discussed under the heading of each special group. The other organs revealed no significant changes. The kidneys remained remarkably free of any significant pathological changes in both the treated and untreated animals.

The pleural, pericardial, and peritoneal cavities contained the normal small amounts of clear fluid, and their surfaces were smooth and glistening. The only exceptions were the pleural cavities in those dogs having an associated secondary bronchopneumonia of streptococcal or staphylococcal origin. In practically all instances the lungs remained pink and air-containing. The spleen was rarely enlarged or involved. The gastrointestinal tract was normal. The pancreas remained intact and revealed no gross or microscopic lesions. The adrenals were of the usual size, cream-colored, firm, and free from lesions. The male genitalia were not involved. The testicles were free of involvement though frequently noted in close proximity to severe edema and necrosis which had spread from the initial site of inoculation. Two of the females had severe endometritis, apparently unrelated to the clostridial infection.

No thrombi were seen in the vascular system and the endothelium remained smooth and glistening.

The thyroid gland remained small in all dogs. It was firm and non-inflamed. The lymph nodes were not enlarged. (One dog had a coincidental generalized lymphosarcoma.) The bone marrow appeared normal in the gross. Only 2 dogs seemed to be anemic; however, no blood studies were carried out.

In the following discussion, it will be assumed that the organs not mentioned were found to be normal or had insignificant changes. Only the inoculated site, the heart, liver, and kidneys will be considered in the tables.

The inoculated site (right posterior thigh muscles) and the areas in close proximity were usually greatly swollen by pockets of gas or severe edema. In some dogs the gas was noted in the form of tiny bubbles throughout the tissues producing the

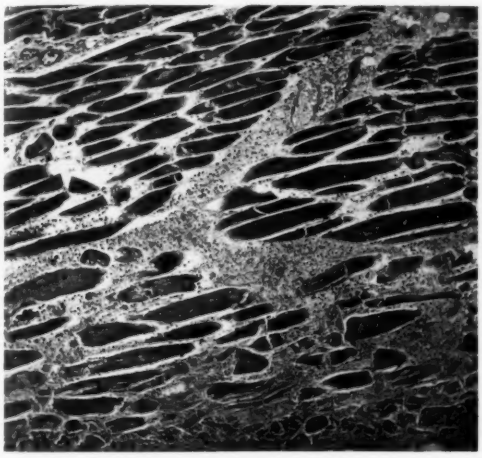

Fig. 5. Skeletal muscle, ×68, at the site of inoculation with a mixed culture (No. 2) of gas gangrene organisms. Dog. No. A-102 (Y8542). This control dog died 27 hours after it had received the inoculation. There are numerous erythrocytes and much fibrin. Examination reveals that the muscle fibers are atrophic and hyalinized. Their nuclei are lost. Edema, inflammatory cells, and pockets of gas are seen.

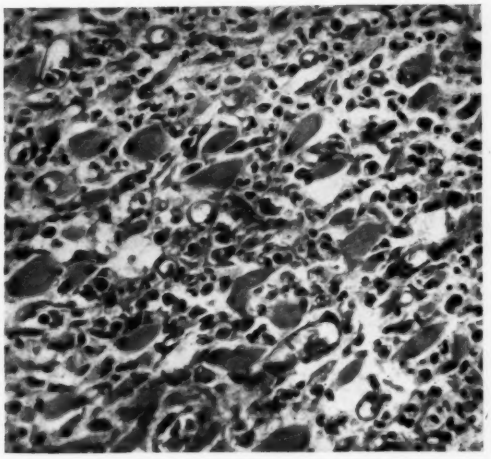

Fig. 6. Skeletal muscle, ×267, at the site of inoculation with a mixed culture (No. 2) of gas gangrene organisms, showing repair. Dog No. AP-12 (Y8674). Therapy used: sodium sulfadiazine, penicillin, and antitoxin. Recovery satisfactory and dog sacrificed 13 days after inoculation. Numerous acute and chronic inflammatory cells and fibroblasts present. Large oval muscle cells are growing and developing new nuclei and show muscle striations.

appearance of a fine sponge. The edema of the muscles consisted of a diffuse dark red serosanguineous fluid. The muscles were mottled and necrotic. Often large pockets containing a dirty gray pus mixed with pieces of necrotic tissue were found. In some of the control animals surviving longer than 36 to 48 hours the muscles were entirely destroyed, leaving intact the skin, blood vessels, nerves, and strands of dense connective tissue. The necrotic process stopped at the attachment of the thigh muscles to the pelvis. In a few animals the abdominal muscles were edematous and mottled with red.

Microscopically, the diseased muscle appeared as a diffuse mass of fibrin and degenerated red blood corpuscles. Only remnants of muscle fibers remained surrounded by connective tissue, and an extensive interstitial edema. Many of the muscle fibers showed a loss of nuclei. Bacilli were often present and small pockets of gas were seen.

THE PATHOLOGICAL CHANGES IN UNTREATED CONTROLS—SEE TABLE I

Infectious agent	Number of dogs
Clostridium welchii (Clostridium perfringens)	5
Clostridium septicum	3
Clostridium novyi	3
Clostridium sordellii (Clostridium bifermentans)	6
Mixed infection #2*	9
Total	26

*Clostridium welchii, Clostridium septicum, Clostridium novyi, Clostridium sordellii, plus Staphylococcus aureus.

The heart was found to be dilated in most of the animals examined post mortem. The walls were moderately thin and the parietal pericardium and endothelial linings were smooth and glistening. The papillary muscles and cords, and the valves were not remarkable. Some heart muscle changes were present in practically every instance. These changes were scattered throughout various parts of the heart muscle and, since the entire heart was not studied under the microscope, we must assume that lesions were often missed. The pathological changes consisted of areas of moderate to severe fragmentation of the muscle fibers with swelling, loss of striations, pallor, fine and coarse granular degeneration. Many of the fibers contained round clear vacuoles. The nuclei showed little change except in rare areas of frank necrosis. Frequently, there were seen scattered areas of Zenker's "waxy degeneration" of the muscle fibers. This consisted of hyalinized areas of muscle which took either an eosinophilic stain or a blue stain. Marked vascular engorgement with red blood corpuscles was common. Some tiny areas of early necrosis and severe edema were found. In dogs which had received therapy, these necrotic areas were seen as small foci of chronic inflammatory cells and fibro-

TABLE I.—UNTREATED DOGS INOCULATED WITH CLOSTRIDIA

Dog No.	Age in years	Time of death in hours post-inoculum	General condition	Pathological changes**				Miscellaneous
				Heart	Leg	Liver	Kidney	
Mixed Culture No. 2								
A-101	2	24	Fair	3	3	1	0	Bulbous vesicles on abdomen
A-102	4	27	Excellent	2	3	1	0	
A-103	4	52	Poor	1	3	1	0	
A-104	1	26	Poor	1	3	2	0	Congestion of lung vessels
A-105	2	25	Excellent	2	3	2	0	
A-106	1	40	Excellent	1	3	2	0	
A-122	4	8	Excellent	2	1	3	0	Bronchopneumonia
A-126	1	12	Excellent	3	3	1	0	
Spc-1	1	40	Excellent	0	3	1	0	Brain stem normal
Clostridium septicum								
A-127	1	48	Excellent	1	3	2	0	Bronchopneumonia
A-128	1	34	Excellent	1	3	3	0	Bronchopneumonia
A-129	1	25	Poor	2	2	1	0	
Clostridium novyi								
A-146	10	50	Excellent	1	3	0	0	Brain stem normal
A-147	12	56	Excellent	1	3	2	0	
A-148	5	29	Excellent	1	3	2	0	
Clostridium sordellii								
P-140	10	55	Good	1	3	1	0	
P-141	3	74	Good	1	3	0	0	
P-142	8	49	Good	1	3	0	0	Brain stem normal
AP-41	1	27	Fair	1	3	2	0	
AP-42	1	28	Fair	1	1	1	0	
AP-43	1	46	Good	0	3	1	0	
Clostridium welchii								
AP-16	6	14	Good	0	3	0	0	
AP-17	1	77	Good	1	3	2	0	Bronchopneumonia; brain stem normal
AP-18	3	32	Fair	1	3	3	0	
P-162	3	15	Excellent	2	3	0	0	
P-163	2	16	Good	2	3	3	1	

**0, No changes; 1, slight change; 2, moderate change; 3, severe change.

blasts with early organization. Cardiac nerve bundles were often seen and were found to show no significant changes.

The liver in all instances was markedly engorged with red blood corpuscles. The sinusoids were greatly distended and the central portions of the lobules were often so distended with red blood corpuscles that the liver cells were flattened and destroyed. Small areas of focal necroses were frequent. In some instances the liver revealed severe generalized damage, as evidenced by marked interstitial edema and large areas of early necrosis. The cells were swollen and their nuclei pale.

Some of the liver cells contained a large vacuole, which was presumed to be a globule of fat. These are seen in normal dogs, but are believed to be an indication of some damage to the metabolic process of the cell.

The kidney contained no notable lesions. Some kidneys showed cloudy swelling and others con-

TABLE II.—DOGS INOCULATED WITH MIXED CULTURE NO. 2 AND GIVEN THERAPY AS INDICATED*

Dog No.	Age in years	Time of death** postinoculum	General condition	Pathological changes***				Miscellaneous
				Heart	Leg	Liver	Kidney	
A. Penicillin alone after 12 hours								
P-110	2	Died 7 d.	Good	1	N	2	1	
B. Penicillin (26,000 units) and sodium sulfadiazine 3 hours postinoculum for 72 hours								
P-101	5	Killed 13 d.	Poor	0	R	1	0	
C. Penicillin (26,000 units) 6 hours postinoculum+1 dose of sodium sulfadiazine 3 hours postinoculum								
P-124	1	Killed 10 d.	Good	1	R	2	0	
P-125	1	Killed 10 d.	Fair	0	R	0	0	
P-128	1	Killed 10 d.	Excellent	0	R	2	0	
P-133	1	Died 7 d.	Fair	0	R	0	0	Fungus bronchopneumonia
P-144	2	Killed 10 d.	Good	0	R	0	0	
P-145	2	Died 28 h.	Excellent	3	N	3	0	Bronchopneumonia
P-148	3	Killed 10 d.	Excellent	0	R	0	0	
P-150	2	Killed 20 d.	Excellent	0	R	0	0	
P-155	3	Killed 20 d.	Excellent	0	R	0	0	
D. Penicillin (14,000 units) 12 hours postinoculum+1 dose sodium sulfadiazine 3 hours postinoculum—8cc/k antitoxin 12 hours postinoculum								
AP-1	1	Killed 13 d.	Good	0	R	1	1	
AP-2	5	Killed 13 d.	Excellent	0	R	0	0	
AP-6	1	Killed 13 d.	Fair	0	R	0	0	
AP-7	3	Killed 13 d.	Good	1	R	0	0	
AP-10	1	Died 12 h.	Good	0	0	0	0	Brain stem normal. ? Anaphylaxis
AP-12	3	Killed 13 d.	Fair	2	R	0	0	
AP-27	10	Died 24 h.	Excellent	2	0	0	0	? Anaphylactic death—Antitoxin
AP-31	1	Killed 12 d.	Fair	0	R	0	0	
AP-32	3	Killed 12 d.	Fair	1	R	0	0	
AP-33	3	Died 10 d.	Fair	1	N	3	0	

*Doses indicated are amounts per kilogram weight of dog
**d—days; h—hours.
***0, No changes; 1, slight changes; 2, moderate changes; 3, severe changes; R, inoculated site shows signs of recovery; H, slight signs of recovery; N—no recovery.

tained tubules which were filled with a fine granular coagulum. In some the blood vessels were engorged with red corpuscles, but neither necrosis nor hemorrhage as seen.

THE PATHOLOGICAL CHANGES IN TREATED ANIMALS

Most of the treated dogs recovered from the gas gangrene infection and, in general, the inoculated site showed remarkable repair of the original severely damaged muscle. Some of the inoculated thighs were practically normal in gross and microscopic appearance. However, they showed microscopic changes indicating obvious severe damage earlier in the course of the disease. Microscopically the leg muscles were filled with acute or chronic inflammatory cells, or both. There were numerous fibroblasts, and new dense connective tissue was being laid down. The fibrin and red blood corpuscles had disappeared. The empty network of connective tissue between the original muscle fibers contained large cells which were eosinophilic and contained a single small oval nucleus. Many of these cells had begun to grow to enormous size and developed a striated cytoplasm as well as several nuclei. This appeared to be muscle regeneration or replacement of destroyed muscle by new muscle fibers. Although the inoculated muscles showed marked disintegration, edema, and areas of necrosis before recovery, they were replaced not by masses of scar tissue but by muscle tissue so that in some dogs the muscles assumed a normal appearance. Further studies of this process are being carried out. The muscle fibers which

TABLE III.—DOGS GIVEN THERAPY ALONE WITHOUT INOCULATION BY CLOSTRIDIA*

Dog No.	Age in years	General condition	Pathological changes				Miscellaneous
			Heart	Leg	Liver	Kidney	
P-107	2	Excellent	0	0	0	0	
P-114	1	Excellent	0	0	0	0	

*This study was conducted to show that there is no incompatability between penicillin and sodium sulfadiazine which could be detected by histological study.

have been partially destroyed by the disease contain more nuclei than are usually seen in normal muscle. These nuclei were also larger than skeletal muscle nuclei.

Frequently the skin overlying the inoculated thigh was necrotic and hung loosely over the thin, atrophic muscles. The latter was cleaned of subcutaneous fascia and all connective tissue coverings. The red muscle shone through a very thin layer of fascia. Each individual muscle lay separate and moved freely.

The heart showed only an occasional area of old necrosis with good organization. Some fragmentation with scattered areas of hyalinization was noted. Those dogs dying in spite of treatment had severe cardiac fragmentation, hyalinization, edema, pallor, loss of striations and marked engorgement of all the blood vessels, especially the arterioles and venules. A few of these animals had a complicating bronchopneumonia. One may postulate that the cardiac damage in these fatalities was a result of the action of the toxin which was formed prior to the institution of adequate therapy, since enough growth of the organism had occurred to cause severe necrosis at the inoculated site.

The liver in general was undamaged. The cells all appeared filled with "foam," which apparently was glycogen and fatty compounds. The cell walls, their nuclei, and their size and shape appeared normal. The sinusoids were moderately engorged with red blood corpuscles. Some of the livers had clumps of chronic inflammatory cells and fibroblasts with organization, indicating that damage had been done in the past and that it had been checked.

The kidney showed no significant damage either as a result of the disease or of the therapeutic agents.

The following animals were all inoculated with mixed culture No. 2. They were treated by the use of penicillin, sodium sulfadiazine and antitoxin, as indicated:

1. *Penicillin alone* (Table II—A). One dog was studied. This dog died 7 days after inoculation. It had some cardiac changes and the leg showed healing. Some liver necrosis was present.

2. *Penicillin and sodium sulfadiazine* (Table II—B and C). Ten dogs have been studied. Eight were killed 10 days following inoculation. One dog showed severe fragmentation of the heart muscle. The heart had no changes in the other animals. One had many small areas of necrosis in the liver. One dog died 7 days following inoculation. This animal had numerous masses of fungi in the lungs causing severe bronchopneumonia. The other organs were intact. One dog died 28 hours after inoculation. There was a marked reaction at the site of the inoculation. This dog had severe cardiac and liver damage, and bronchopneumonia. In all of the recovered animals the inoculated sites were well healed and no kidney changes were present.

3. *Penicillin plus sodium sulfadiazine plus antitoxin* (Table II—D). Ten dogs were studied. Seven of the dogs were killed within 12 to 13 days after inoculation. Only 1 of these dogs showed significant cardiac damage. The inoculated sites were well healed and no changes were seen in the other organs. One dog died 10 days after inoculation and it showed severe edema and focal necrosis of the liver. The heart muscle had small areas of hyalinization. The inoculated site had a large abscess.

Two of the dogs died within a few minutes after being given intravenous clostridial antitoxin. An autopsy was done immediately after they stopped breathing and no pulse was felt. The auricles were still contracting feebly, indicating that the nerve bundles of the heart were not disturbed. One dog had moderate cardiac changes. There were no changes in any of the other organs and no thrombi were seen. The lungs had tiny emphysematous blebs throughout. Thus, death was probably due to anaphylactoid shock.

4. *Sodium sulfadiazine three hours after inoculation (one dose) plus antitoxin twelve hours after inoculation* (Table IV—A). Nine dogs were studied; all but 2 were killed after 10 days. These showed that the inoculated sites had received severe damage but were being repaired. The disease was under control. The heart showed only slight changes in 2 dogs. Three dogs had small foci of necrosis in the liver.

TABLE IV.—DOGS INOCULATED WITH MIXED CULTURE NO. 2 AND GIVEN THERAPY AS INDICATED*

Dog No.	Age in Years	Time of death** postinoculum	General condition	Pathological changes***				Miscellaneous
				Heart	Leg	Liver	Kidney	
A. Sodium sulfadiazine (1 dose) after 3 hours and antitoxin after 12 hours (16 cc/k in 8 hours)								
A-68	1	Killed 12 d.	Poor	0	R	3	0	
A-78	1	Killed 12 d.	Poor	0	R	1	1	
A-79	7	Killed 12 d.	Excellent	0	R	0	0	
A-90	1	Died 9 d.	Good	3	R	2	0	
A-93	5	Killed 13 d.	Poor	1	R	0	0	
A-94	1	Killed 10 d.	Good	1	R	1	0	
A-99	2	Died 6 d.	Poor	0	N	2	0	Severe bronchopneumonia
A-97	2	Killed 10 d.	Fair	0	R	0	0	
A-100	10	Killed 10 d.	Fair	0	R	0	0	
B. Sodium sulfadiazine after 3 hours for 72 hours and antitoxin after 12 hours (16 cc/k in 8 hours)								
A-107	2	Killed 14 d.	Good	0	R	0	0	
A-109	1	Killed 11 d.	Fair	0	R	0	0	Acute endometritis
A-110	1	Killed 11 d.	Excellent	0	R	0	0	
A-111	1	Killed 11 d.	Good	0	R	0	0	
A-114	2	Died 4 d.	Excellent	1	H	1	0	
A-116	3	Killed 13 d.	Good	0	R	0	0	
A-118	7	Killed 13 d.	Good	2	H	0	0	
A-130	1	Killed 11 d.	Good	0	R	0	0	
A-131	1	Killed 11 d.	Excellent	1	R	2	0	
A-133	10	Killed 11 d.	Excellent	0	R	0	0	Generalized early lymphosarcoma
A-134	10	Killed 11 d.	Excellent	0	R	1	0	
A-135	2	Died 10 d.	Poor	3	H	1	0	Brain stem, spinal fluid—0
A-141	1	Died 7 d.	Good	Postmortem changes. No gross changes. Lungs normal				

*Doses indicated are amounts per kilogram weight of dog.
**d, days
***0, No changes; 1, slight changes; 2, moderate changes; 3. severe changes; R, inoculated site shows signs of recovery; H, slight signs of recovery; N, no recovery.
The liver in most cases was engorged by red blood corpuscles.

Two of these 9 dogs died after 9 and 6 days, respectively. These also showed some recovery of the inoculated site, but one revealed severe cardiac damage, and the other dog had bronchopneumonia. Both had moderate damage in the liver.

5. Sodium sulfadiazine three hours after inoculation for seventy-two hours, plus antitoxin twelve hours after inoculation (Table IV—B). Thirteen of these dogs were studied. Only 1 showed significant cardiac damage. All of the animals showed good healing and recovery at the inoculated sites. No significant pathological changes were seen in the other organs.

Three died in 4, 7, and 10 days, respectively. Two had severe cardiac damage and some liver damage. The sites of inoculation were healing well.

SUMMARY

In general, the untreated dogs receiving a mixed culture of gas gangrene organisms (No. 2) showed more severe damage than did those animals receiving a single pure culture of one of the clostridia studied. We were unable to determine any difference in degree of damage caused by the various pure cultures of the individual clostridial organisms. The pathological studies revealed that the infection was severe and that extensive damage was always produced at the site of inoculum.

All but 3 of the control dogs showed some cardiac damage. Liver damage was considerable. The brain stem and spinal fluid were studied in 4 dogs with negative results. The other organs, including the kidneys, were undamaged. Four of the dogs had bronchopneumonia.

The untreated animals showed excellent recovery of the inoculated site. In most instances cardiac damage was prevented. The liver received only minor injury in most dogs. The few animals dying as a result of the infection despite therapeutic measures revealed cardiac damage and complications. The kidneys were unaltered by disease or therapy. Two dogs died an anaphylactoid death presumably from antitoxin therapy.

Most authorities agree that death in clostridial infections is toxic in nature. Our experimental studies would bear this out. The mechanism of death is not agreed upon by the various writers. Our studies indicate that, with the exception of the local site of the infection, the heart and liver (in the order named) are the organs most frequently and most severely involved. The rôle of liver damage as a cause of death in our animals cannot be fully evaluated as blood chemistry studies were not done. No definite kidney damage could be found as a result of the disease or the treatment.

REFERENCES

1. Bengtson, Ida A. Public Health Reports. 1934, 49: 251–262, 1557–1569.
2. Callander, C. Latimer, Haim, Arthur, and Maximov, Alexis. Am. J. Surg., 1938, 42: 811–823.
3. Dowdy, Andrew H., and Sewell, Robert L. Radiology, 1941, 37: 440–442.
4. Eliason, Eldrige L., Erb, William H., and Gilbert, Philip D. Surg. Gyn. Obst., 1937, 64: 1005–1014.
5. Forbus, Wiley D. Arch Path., 1926, 2: 318–339.
6. Idem. Arch. Path., 1926, 2: 486–499.
7. Ireland, M. W., and Coupal, James F. Med. Dept. U. S. Army in World War, 1929, 12: 407–567.
8. Kaufman, Edward, and Reiman, Stanley P. Pathology Text. Vol. 3, 2042–2045. Philadelphia: P. Blakinston's Son & Co., 1929.
9. Kirby, E. Beitr. path. Anat., 1892, 11: 302–322.
10. Lautenschlager, Ludwig. Arch. exp. Path., Lpz., 1920, 85: 1–31.
11. Olafson, Peter. Personal communications.
12. Pasternack, Joseph G., and Bengtson, Ida A. National Institute of Health Bulletin No. 168, 1936, 1–46.
13. Robertson, Muriel. J. Path. Bact., Lond., 1920, 23: 153–170.
14. Sewell, Robert L. N. York State J. M., 1940, 40: 57–58.
15. Straub, Walther. Münch. med. Wschr., 1919 66: 89–91.
16. Volkmann, Rudolf. Beitr. path. Anat., 1893, 12: 233–332.
17. Welch, William H. Bull. Johns Hopkins Hosp., 1900, 11: 185–204.

PRIMARY CARCINOMA OF THE EXTREMITY

HAROLD M. CLARKE, M.D., St. Louis, Missouri

A STUDY of primary carcinoma of the extremity seen at the Barnard Free Skin and Cancer Hospital from 1925 to 1940 has been made, and the results of this study are presented here.

The series comprises 214 cases, which is 4 per cent of an estimated 5,000 cases of skin cancer recorded at this clinic during this period. Of the 214 cases, in only 15 per cent was the lower extremity affected as compared with 85 per cent for the upper extremity. This ratio is comparable to that found by other observers. Of the 182 cases of upper extremity carcinoma, 132 occurred in males and 50 in females, whereas in the lower extremity there were 23 cases in males and 9 in females. The lesion affected the right extremity in 94 cases as compared with the left in 88 cases; the right lower extremity in 15 cases and the left lower extremity in 17 cases. The lesion of the upper extremity is definitely one of advanced age as the maximum incidence occurred in the group of patients 70 years of age or older. This is in contrast to the maximum incidence of cancer elsewhere (on the skin) as then the maximum incidence is found to be in an earlier age group. The incidence of lower extremity carcinoma is greatest in the group 50 to 60 years of age.

In the entire series there was but 1 negro who had a primary carcinoma of the extremity—a squamous cell lesion of the leg. This 1 case is not a true indication of the frequency of the disease in negroes in general as negroes comprised less than 5 per cent of the patients seen in this clinic. There is some indication that the incidence of skin cancer on unexposed portions of the bodies of negroes does not differ remarkably from the incidence on unexposed parts of whites.

On the upper extremity, as in other series, the preponderance of lesions occurred on the dorsum of the hand. There were 150 lesions of the hand, 24 of the arm, and 9 of the fingers. Four of the lower extremity lesions occurred on the toes, 6 on the foot, and 22 on the leg.

In general, the various precancerous conditions which have been known to precede cutaneous carcinoma, apply as well to extremity carcinoma. A classification of etiological factors has been offered by Mason as follows:

I. Carcinomas arising in connection with trauma or irritation:
   a. Irradiation
      X-ray
      Radium
      Solar (such as exemplified by senile keratoses, keratoses in sailors, farmers, etc.)
   b. Chemical irritation, external (e.g., tar, anilin, pitch, etc.)
      Internal (arsenic)
   c. Chronic mechanical irritation
   d. Scar tissue irritation (burn scar especially)
   e. Irritation from a single trauma or chronic infection, syphilitic ulcer, varicose ulcer, etc.
II. Carcinoma arising in some previous skin tumor
III. Carcinoma arising from normal skin

In this clinic, serving largely a rural population, a great many cancers have occurred as a result of exposure to solar radiation, for example in farmers or patients presenting sailor's skin. Of the 182 patients with upper extremity lesions, 72 gave a history of being farmers or had been engaged in outdoor occupations; 59 exhibited or gave a history of pre-existing keratoses and 50 had already either experienced or subsequently developed another cutaneous cancer. This high incidence of multiple lesions has not been noted in other studies of the subject.

The histories studied gave few clues to other etiological factors. No patient developed carcinoma as a result of x-radiation, a relatively frequent etiological factor in many clinics. One patient gave a brief history of working with tar. Five patients gave a history of a single trauma as the etiological factor. On the upper extremity, in 2 cases carcinoma developed in old scars, and on the lower extremity, in 4 cases carcinoma occurred in old scars, one of them a burn scar. No definite mechanical factor as a possible cause of the lesion was found in this series; neither was chronic irritation an important factor. In none of the cases was carcinoma found in old osteomyelitis sinuses, sites occasionally reported by other observers. Arsenical keratosis has been considered as an etiological factor; 14 of 312 cases of extremity carcinoma reported by Taylor, Nathanson, and Shaw were preceded by arsenical keratoses. Although it is not an uncommon finding in other clinics, epidermal carcinoma developing on the basis of arsenical keratosis has not been seen either

From the service of Dr. W. E. Leighton, Barnard Free Skin and Cancer Hospital. Dr. Clarke is a trainee of National Cancer Institute.

in the surgical or dermatological departments of this hospital. There was but 1 case of cutaneous cancer which developed in a lupus scar, but this cancer was not of the extremity. Lupus as a precursor of cancer is also a more frequent finding in other clinics. Mundelein, in a series of 2,557 cases of lupus, reported 83 cases of cancer. The development of cancer on a pre-existing benign lesion was not definitely demonstrated in any of our cases, but in 4 patients the very long history (20 years) suggested this etiological factor.

The diagnosing of cutaneous carcinoma offered little difficulty. Almost invariably it was made on examination of patient. The presence of a malignant lesion developing in a chronic ulcer or old sinus tract was not so readily determined; in some instances an infected epithelioma closely resembled a granuloma. In such cases a biopsy was made to establish the diagnosis.

The malignant lesion of the extremity is usually a squamous cell carcinoma. There were 163 such lesions of the upper extremity as compared with 18 basal cell lesions. There were only 3 basal cell tumors of the lower extremity and 28 squamous cell lesions. This ratio is not at variance with that found by other observers. The basal cell lesions developed at an earlier age than did the squamous cell tumors. There was one sweat gland carcinoma in this series and one basosquamous cell lesion. The great majority of the squamous cell tumors have been of low grade malignancy. In this study, there were but 4 lesions which could be classified as Broders' group III and one in the group IV classification. All other squamous cell lesions could be classified in either group I or group II. Low grade malignancy has been found characteristic of carcinoma of the extremity in other reports; 97 per cent were group I or II in DeBell and Stevenson's series.

The treatment of all but 7 of the local lesions was surgical and consisted of either local excision or amputation, depending on the extent of involvement. In general, the decision to perform an amputation rested upon the amount of fixation of the lesion. Even though there was obvious regional lymph node involvement, amputation was not done if the local lesion was not fixed. Extensive superficial lesions have been locally excised with good results, and on several occasions, lesions which were only slightly fixed to the underlying structures, were locally excised with resulting cure. These latter types of lesions were excised with cautery. It was also the practice to use the cautery for sloughing, necrotic, infected, ulcerated lesions. If a defect was not amenable to immediate closure, the defect was covered with a split graft, immediately if the lesion was clean, or after a suitable bed of granulations had been established, when it had been necessary to resort to cautery. There have been only 6 local recurrences following local excision in this series. One fatal outcome followed local recurrence, and in 1 case the second operative effort consisted of an amputation. Five of the local lesions were treated by radium with 3 local recurrences resulting, and 1 lesion treated with x-ray promptly recurred. With more adequate dosage and present day methods of radiation, however, x-radiation should give good results in superficial lesions.

The criterion for amputation, with rare exception, was fixation of the lesion. The site of amputation, when it was required, was determined by the requirements of satisfactory margin and good function. If there was clinical involvement of the epitrochlear or popliteal space, the chosen site of amputation was above the elbow or the knee. In 2 patients who had extensive axillary involvement, with fixed nodes, shoulder girdle amputations were done. One of these patients died after operation, the other died in 1 year, of carcinomatosis.

The proper handling of the lymphatic drainage areas of the extremities is the most perplexing problem offered in connection with the treatment of carcinoma of the extremity. In general, it may be said that in this series lymph node dissections were not done unless there were clinically involved nodes.

In this series the analysis of the lymph node involvement is as follows: in 14 patients of 136 with upper extremity lesions which could be followed 4 years or more, the lymph nodes were noted as being 2 centimeters or larger when first seen; in 15 patients they were between 1 and 2 centimeters and in the remaining 107 they were either not recorded as being palpable, or were less than 1 centimeter in size. Of this latter group, 6 patients subsequently developed suspicious axillary nodes, and of these 6, 3 patients subsequently died of the disease. Two of these 3 patients were not faithful in their check-up visits at the clinic, and when they finally presented themselves for operation, their nodes were between 5 and 6 centimeters in the greatest dimension and were partially fixed. The third case had a prompt axillary dissection when it was noted that the axillary nodes were enlarging. He had a Broders' group III lesion and died of generalized carcinomatosis in 2 years. In the group with nodes 1 to 2 centimeters in size there were 5 patients on whom axillary dissections were done. Only 1 of these 5 had positive nodes, and in this patient the nodes were described as

stony hard and were very suspicious clinically. In the third group, 8 were subjected to axillary dissection, and of these 7 had positive nodes. In 2, axillary dissection was deferred to a second stage because of debilitation of the patient, and subsequent to the removal of the primary lesion, the nodes subsided and have remained nonsuspicious. One refused operation, 1 was considered inoperable, and 2 had extensive fixed nodes and were subjected to shoulder girdle amputation. Of the entire group, only 6 patients who were thought to have no nodal involvement when first seen, subsequently developed nodes which were thought to be clinically positive, and of this group only 4 actually proved positive. Three of these 4, as pointed out, died of the disease.

Of the group of lower extremity carcinoma (32 cases), 5 patients had nodes 2 centimeters or larger when first seen, 3 had nodes between 1 to 2 centimeters, and the remainder had nodes 1 centimeter or less. Four of the 5 with large nodes were subjected to inguinal dissection, and all proved to have positive nodes. The nodes of the fifth patient subsided after removal of the local lesion. One patient with nodes between 1 and 2 centimeters was subjected to an inguinal dissection which revealed positive nodes. Two patients with stony hard 1 centimeter nodes had inguinal dissections, but their nodes were negative. An expectant attitude was adopted regarding the remainder, of whom one patient subsequently developed clinically positive nodes. This patient deferred surgery for 9 months after it was advised, and died after operation of hemorrhage. At operation the nodes had been found to be matted and firmly attached to the femoral vessels.

It may be said then, that in this series, 4 patients died who might have been saved by doing a "prophylactic" node dissection. This statement should be qualified by the information that 3 of the 4 patients were unco-operative in returning to the clinic for check-up, so that surgery was deferred beyond the time when it would ordinarily be recommended.

No iron clad rule should be adopted in regard to the treatment of axillary or inguinal nodes. For most patients the concept of performing axillary node dissections only when enlarging or persistently enlarged nodes (i. e. nodes which remain enlarged after the removal of the primary lesion) are present, would seem to be a good one. The grade, size, duration, precursor of the lesion, and the age of the patient are factors, however, that should be considered when making a decision regarding the treatment of the lymphatic drainage areas. It would be reasonable, for example, to perform an axillary dissection on a relatively young individual with a fixed grade III lesion of his hand, even though no nodes were palpable. It is also reasonable to perform axillary dissections regardless of the clinical state of the axilla, if there is epitrochlear involvement.

A more radical attitude may be adopted regarding the treatment of involvement of the inguinal nodes. There appear to be good reasons for this: First the percentage of inguinal lymph node involvement in our series was high as compared to that of the upper extremity. Six of the 22 cases which we were able to follow satisfactorily had positive inguinal lymph node involvement or subsequently developed it. Second, the prognosis, if inguinal lymph nodes are involved, is very poor, as demonstrated in the series of Taylor, Nathanson, and Shaw, and in our own series. Third, lower extremity carcinoma occurs in a younger age group and more radical attempts to eradicate it are justified.

Many surgeons have adopted a conservative attitude in regard to the treatment of lymph node involvement, i.e., they advise node dissection for persistently palpable nodes. Still others present figures which are not quite so convincing as to the value of the conservative attitude. Taylor, Nathanson, and Shaw, report that axillary metastases subsequently developed in 11 per cent of 154 cases with nodes less than 1 centimeter when first seen. Pack has stated that the 24 per cent of patients admitted to the Memorial Hospital with epidermoid cancer of the extremity, without evidence of regional lymph node involvement, subsequently developed lymph node metastases. It must be remembered that the series at the Barnard Free Skin and Cancer Hospital, with the exceptions noted, is composed of malignant lesions which had as percursors sailor's skin or senile keratoses, or the lesions developed upon previously normal skin. There is some indication that such carcinomas of the extremity, that is, carcinomas which have as percursors sailor's skin or senile keratosis, are less malignant than those which develop on certain other etiological bases; for example in Taylor, Nathanson and Shaw's series, 30 per cent of the cases developing in burn scars, 30 per cent of those developing in varicose ulcers (a comparatively rare site of extremity carcinoma), and 21 per cent of lesions developing as a result of arsenical keratoses, exhibited lymph node metastasis. Handley advises radical removal of lymph nodes in all cases of roentgen carcinoma, so frequently did he find that lymph node metastasis developed from roentgen carcinoma.

The prognosis of the disease, as shown in this series, has been good in regard to the upper extremity, but less favorable in regard to the lower extremity. Of our 182 upper extremity cases, 9 died of the disease, 112 were followed 5 years or more without evidence of the disease, 15 were followed 4 years without evidence of disease, and 46 patients could not be followed. In the followed group of 136 cases the survival rate was 93 per cent. The prognosis, as would be expected, was less favorable if there was lymph node involvement. Of 11 axillary dissections revealing positive nodes, 3 died of the disease, 6 remained well, 2 were not followed—a survival rate of 66 per cent, excluding the cases that could not be followed.

In the lower extremities, 10 cases could not be followed. Of the 22 remaining, 6 died of the disease, 2 were free from disease 4 years after treatment, and 14 were well 5 years or more after treatment. The survival rate was 70 per cent. Of those with positive inguinal nodes who had inguinal dissection, only 1 of the 5 patients who could be followed, survived.

There are few published 5 year end-result figures for extremity carcinoma. Other reports in general indicate a higher mortality, which could be estimated at double that which we have reported, with a similar ratio between the degree of malignancy of the upper and lower extremity lesions. This difference could possibly be ascribed to varying etiological factors, as the treatment in the larger reported series has not been materially different from the treatment at this clinic. The effect of lymph node involvement on prognosis is similar in other series to that reported here. Pack reports 17 axillary dissections revealing positive nodes, with 35 per cent mortality, and 7 inguinal dissections with 38 per cent mortality from the disease, with 2 patients not followed for 5 years. Taylor, Nathanson, and Shaw report 21 axillary dissections with positive nodes, with only 9 cures, and of 14 patients with positive inguinal nodes, only 2 were known to have survived.

CONCLUSIONS

1. Primary carcinoma of the upper extremity is of considerably more frequent occurrence than primary carcinoma of the lower extremity. On the upper extremity the maximum incidence is in a later age group.

2. Squamous cell carcinoma on the extremity occurs approximately eight times more frequently than does basal cell carcinoma. The lesion is characteristically of low grade malignancy.

3. The treatment of superficial or slightly fixed lesions is local excision. Amputation is indicated for extensive and fixed lesions.

4. Regional lymph node dissection is always indicated in the presence of persistently enlarged or enlarging nodes. In some instances, lymph node dissection may be indicated in the absence of palpable nodes.

REFERENCES

1. Adair, F. E. Surg. Clin. N. America, 1933, 13: 423–430.
2. Bick, E. M. Ann. Surg., 1936, 102: 410–414.
3. Charache, H. Surg. Gyn. Obst., 1939, 68: 1002–1006.
4. DeAsis, C. Ann. Surg., 1926, 83: 663.
5. DeBell, P. J., and Stevenson, T. D. Surg. Gyn. Obst., 1936, 58: 222–229.
6. Handley, W. S. Lancet, 1934, 1: 120–122.
7. Mason, M. L. Surgery, 1939, 5: 27–46.
8. Mundelein, W. Die Prognose des Lupuscarcinoms, Inaugural Diss., Münster, i. W., 1935.
9. Pack, G. T. Surgery, 1939, 5: 1.
10. Perez, R. F. Jr. Am. J. Surg., 1929, 6: 545.
11. Taylor, G. W., Nathanson, I. T., and Shaw, D. T. Ann. Surg., 1941, 113: 268.

EDITORIALS

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THE ULCER CARCINOMA PROBLEM OF THE STOMACH

BECAUSE many surgeons have shared an indomitable conviction that carcinoma of the stomach is relatively curable by early resection, cures in the terms of living and well two, five, ten, and even twenty years following operation have been reported in increasing volume from many clinics. This accomplishment and the prospect of increased salvage in the future are the result of two factors: a progressive reduction in operative mortality and a progressive increase in the number of early resectable cases. The former is for the most part an accomplished fact with surgeons of large experience in this type of surgery. Thus, until some form of treatment which offers more than surgical resection is forthcoming, progress will result principally from contributions which will serve to shorten the interval between the inception of the neoplasm and the recognition of its presence. By the word, "inception," it is intended to imply the not improbable development of a means by which the presence of neoplastic tissue can be detected before it gives rise to symptoms. At present, progress will depend upon factors which will shorten the interval between the onset of symptoms and the recognition of the disease. These factors concern mainly medical and lay education. Compared to this potential source of benefit the salvage to be derived from such future contributions as will effect a further reduction of operative mortality is insignificant.

The delay in the recognition of carcinoma of the stomach has been attributed much too generously to the patient's indifference to his symptoms and reluctance to consult a physician. Unfortunately, the evidence in the majority of instances also incriminates the medical profession. This is attributable to certain misconceptions regarding the disease. It is not generally appreciated that despite every available means of diagnosis it is impossible in an astonishingly large percentage of cases to differentiate early carcinoma of the stomach from benign gastric ulcer. This fact and its importance in respect to early diagnosis and treatment has been brought out in the singularly important publications of Allen and Welch[1] and of Walters, Gray, and Priestley. From a study of two thousand four hundred and sixty-nine cases of carcinoma of the stomach at the Mayo Clinic Walters, Gray, and Priestley[2] found that thirty-seven per cent of the patients who had operable carcinomas of the stomach and twenty-five per cent of patients with inoperable lesions gave histories that were typical of benign ulcer, and, furthermore, the distressing fact that eighty per cent of the patients with carcinoma of the stomach

[1] Ann. Surg., 1941, 114:498.
[2] Tr. West. Surg. Ass., 1940, p. 200.

who gave typical ulcer histories gained temporary relief of symptoms from medical management. Unfortunately, relief on an ulcer regimen is often interpreted by both the physician and patient as confirmatory evidence of the benign character of the lesion, with the result that definitive treatment is delayed and the patient's chance of cure correspondingly reduced. The patient relieved of distress is likely to disregard instruction to return for follow-up observation until symptoms recur.

In the same series of cases these authors found that by x-ray study the diagnostic error was reduced to ten per cent; that is, in ten per cent of the cases the roentgenologists diagnosed carcinomatous lesions as benign ulcers. In an additional fourteen per cent of cases they stated that the diagnosis was indeterminate.

Similarly, Allen and Welch reported two hundred and seventy-seven cases which had been diagnosed and treated as gastric ulcers at the Massachusetts General Hospital. In this series there were thirty-nine cases in which the ulcers subsequently were proved to be carcinomatous, an error of fourteen per cent.

The advantage to be gained from resecting carcinomas when they are indistinguishable from benign ulcers is brought out emphatically by Allen and Welch. In a series of thirty cases in which the preoperative diagnosis was benign ulcer but in which the resected specimens proved to be carcinoma, forty per cent were living and well five years after operation. These results were compared with those obtained in ninety-three cases in which resections were done for lesions which were obviously carcinoma preoperatively. Only twenty per cent of this series was living and well at the end of five years.

How is it possible to salvage by early resection this sizable important group of cases which masquerade as benign ulcers? To reach the largest number of cases at the earliest and most favorable time would necessitate resection of all ulcerating lesions of the stomach. This radical principle is not without its advocates, and there is prospect that as the number of competent resectionists increases it will receive rather general acceptance.

Obviously, the application of this principle would result in the resection of many uncomplicated benign ulcers, but this is acceptable in the minds of the advocates of the principle on the basis that benign, gastric ulcers as a group are better treated by resection. This opinion is held with due respect to operative mortality which, in experienced hands, is insignificant compared to the normal mortality from complications as hemorrhage, obstruction, and perforation. Furthermore, if some of the carcinomas arise in chronic benign ulcers then resection of ulcers may, on occasion, have prophylactic merit.

A more conservative but less certain and less expeditious method is that of clinical trial. By this method all questionable cases are placed on a rigid ulcer regimen, preferably with bed rest for a period of three weeks. At the end of this time all patients who fail to obtain relief should be resected without delay. Certain of these refractory cases are benign ulcers but are sufficiently intractable to necessitate resection. All remaining patients, without exception and irrespective of relief of symptoms, should be re-examined roentgenographically. The patient must be impressed with the necessity of re-examination and with the fact that relief of symptoms on an ulcer regimen does not preclude the possibility of a malignant tumor. Carcinoma can be excluded with certainty only by evidence of progressive and final healing of the lesion in serial roentgenographic studies. It is not enough to demonstrate merely a reduction in the size of a crater but it is obligatory to carry out roent-

genographic examinations every 2 weeks thereafter, until all evidence of the ulcer crater has disappeared. An ulcer regimen may cause a reduction in the inflammatory reaction around a carcinomatous ulcer and create the illusion that the crater has become more shallow and smaller. After an experience of this sort the writer has insisted upon a complete roentgenographic follow-up.

It goes without saying that all lesions which fail to regress or fail to heal after an initial regression should be resected.

Various criteria have been offered to aid in the differential diagnosis of ulcer and carcinoma, such as the age of the patient, the duration of symptoms in respect to the patient's age, the location of the lesion in the stomach, the size of the crater and gastric acidity. Unfortunately, there are too many exceptions to each of these criteria for them to be relied upon in making a vital decision in the individual case. Gastroscopy is of no help because it provides merely the observer's visual impression which at best lacks the precision necessary in dealing with carcinoma. This problem can be decided on no less precise evidence than that provided by biopsy and, until tissue can be obtained by other means, it will be necessary to continue exploratory operations.

In summary, it may be stated that the prevailing defeatist attitude in respect to carcinoma of the stomach is unwarranted. To be sure, there is a small group of cases which from the beginning are hopeless. The tumors in this group metastasize early and, presumably in some instances, before the local lesion gives rise to symptoms. Of the other cases the majority reach the surgeon several months or even years after the onset of symptoms. Most of them have been treated as peptic ulcers or as achlorhydric or other forms of dyspepsia and in the majority of instances treatment has been administered without recourse to roentgenographic investigation. In addition to this large neglected group, there are the cases in which every available means of investigation fails to differentiate the malignant from the benign ulcer.

The problem of carcinoma of the stomach is in general a challenge to diagnostic acumen for in proportion to its improvement the number of long term cures will increase.

J. Dewey Bisgard

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

THE present edition of Osler[1] brings up to date a textbook which was designed for the use of practitioners and students and has gone through fifteen editions since 1892. The present author under whose direction three editions have been published has lived up to the Oslerian tradition by presenting from personal observation clinical descriptions of most diseases. Some 780 medical entities are grouped in an orderly index and detailed within the 1498 pages of this book.

Notable among the additions in this volume is a chapter on aviation medicine, dealing with the effects of high altitude, high speed, cold, and wind on the human organism. The inclusion of such uncommon diseases as ornithosis and phlebotomus fever shows the importance of domestic fowl and insects as vectors in the dissemination of virus infections.

Sulfonamides are given more consideration in the treatment of pyogenic infections. Unfortunately this book went to press before penicillin became available to the medical profession, consequently the information on this drug is incomplete.

No textbook in medicine is written for a larger group of readers. The practitioners will appreciate this work for its uniformity and high quality, and will value the carefully selected and informative references. As a textbook it would have more appeal to the student of medicine if less effort were directed at encyclopedic completeness and more illustrations were used. It can be well recommended to all.

HOWARD B. CARROLL.

IN his book *Vascular Responses in the Extremities of Man in Health and Disease*[2] Dr. Abramson has uniquely brought together physiological concepts and methods of examination of the circulation in the extremities in health and disease and has evaluated very fairly both methods and results. His approach to the problem is stimulating, interesting, succinct, and the subject matter is so clearly stated that it is easy for the student and clinician to grasp. The quantitative methods of examination are described in detail. He stresses particularly, the venous occlusion plethysmographic method of studying the rate of peripheral blood flow, yet is fair in stating the necessary precautions for accuracy and the factors limiting its usefulness.

The chapters devoted to anatomy, physiology, and the nervous control of blood vessels contain epitomized essentials which make them ready references for students and collateral reading. His summary of quantitative procedures in the study of blood vessels and the rate of peripheral blood flow is useful and from a practical standpoint in general use; the reviewer is particularly in accord with his recommendation of peripheral nerve block for practical purposes as compared to lumbar and dorsal sympathetic block in studying temperature responses of the extremities in occlusive and spastic vascular disease. Peripheral nerve block is simple and without danger. Spinal anesthesia, lumbar and dorsal sympathetic and brachial plexus novocain infiltrations are technically more difficult, anesthesia less often completely accomplished, fraught with more accidents, and the added information rarely justifies the use of the more complicated procedures.

He has considered the physiological functions of ingestion of food, menses, gestation, anoxia, and effect upon peripheral blood flow interestingly, and quotes other experiences extensively before stating his conclusions.

Pharmacologic agents, hormones, insulin, histamine, acetyl choline, prostigmine, neosynephrin, paredrinol, paredrine, tobacco, ergotamine tartrate, renin and angiotonin, and anesthetic agents are considered, and the literature to date reviewed.

Blood flow in abnormal states, including metabolic, systemic, blood, cardiac, and neurologic disorders are briefly but completely discussed combining their physiological interpretation with their clinical manifestations.

The functional and organic vascular disease of the arteries and veins and the evaluation of methods used in their treatment are discussed in keeping with the latest clinical conceptions of pathology and therapy.

The style of the book is engaging, simple, compact, and its ease of reading is gratifying, for its contents are such that they might have been technically confusing.

The references at the end of each chapter are extensive. The book is a great source of material for students and clinicians interested in this problem.

BEVERLY CHEW SMITH.

THE book entitled *Female Endocrinology*[3] by Jacob Hoffman is a useful reference work of physiological and clinical literature in endocrinology.

[1] THE PRINCIPLES AND PRACTICE OF MEDICINE; Originally written by Sir William Osler, Bart., M.D., F.R.C.P., F.R.S. Designed for the Use of Practitioners and Students of Medicine. By Henry A. Christian, A.M., M.D., LL.D., (Hon.) ScD., Hon. F.R.C.P.(Can.), F.A.C.P. 15th ed. New York and London: D. Appleton-Century Co., Inc., 1944.

[2] VASCULAR RESPONSES IN THE EXTREMITIES OF MAN IN HEALTH AND DISEASE. By David I. Abramson, M.D., F.A.C.P. Chicago, Ill.: The University of Chicago Press, 1944.

[3] FEMALE ENDOCRINOLOGY INCLUDING SECTIONS ON THE MALE. By Jacob Hoffman, A.B., M.D. Philadelphia and London: W. B. Saunders Co., 1944.

Approximately half of the book is taken up with a review of endocrine physiology according to organs, while the second half is concerned with clinical endocrinopathy. A third section is devoted to laboratory methods and results. A bibliography of references is appended to each chapter of each section.

The author's personal testimony on endocrine treatment is to be commended for its honesty and conservatism. When quoting the literature the author has a tendency to report the claims of older papers. Such and such a writer stated that this or that endocrine treatment was successful. In this way, many uncorroborated claims are perpetuated. It is apparent from a historical point of view that many therapeutic trials are reported in the course of medical history, which later are found to be completely irrelevant when the true treatment is discovered. Textbooks and reference works have a tendency to cherish these abortions and preserve them, much to the confusion of the uninformed reader and to the indefinite extension of bibliographies. Such compilations should be confined to medical history.

The reviewer has the impression that the great fields of growth and maturation have been neglected. Adolescence is covered in five pages and no systematic discussion of growth appears in any section. In the discussion of obesity, the psychosomatic aspect of this condition is not emphasized. The estrogenic control of menopausal symptoms seems to the reviewer to be unnecessarily discounted. In certain cases it is definitely specific and remarkably effective.

In general, one might say that such a book does accumulate much valuable material and gives many references which may or may not be valuable; that it fails to give practical directions to the clinician since the discussion usually ends in a nebulous argument pro and con; and that neither endocrinology nor medical gynecology receive adequate presentation.

PAUL STARR.

THE excellent book *Industrial Ophthalmology*[1] by Hedwig Kuhn will be of great value to ophthalmologists engaging in industrial work. It is the first comprehensive treatise that has been published dealing with industrial ophthalmology as a special field. In this book the author attempts to correlate the essential information relating to the visual problems of the worker and his job.

A whole chapter is devoted to visual testing in industry. It starts with the problem of job analysis which is the appraisal of a specific job as it applies to the demands made upon the eye during the performance of the work. From the standpoint of examination the tests may be divided into pre-employment, periodic rechecks, and general surveys. The standard basic visual data needed are visual acuity for distance and near, with and without glasses, stereopsis, muscle balance, and color appreciation.

The correction of visual defects for the job is discussed at some length, and here the author shows the value of expert advice in increasing the production and the prevention of accidents.

Dr. Albert Snell has contributed an excellent chapter on industrial eye injuries caused by solid bodies. This chapter includes a description and classification of eye injuries together with their treatment and complications. The chapter on eye protection lists the types of goggles available and discusses a goggle program which even includes filling and servicing by a plant optician.

Welding, flash conjunctivitis and epidemic keratoconjunctivitis are discussed in the chapter on recent developments as they are related to industrial eye problems.

The appendix is devoted to toxic hazards with a glossary of terms. There is also an outline for an industrial eye program, and the appraisal of loss of visual efficiency as approved by the Section on Ophthalmology of the American Medical Association in June, 1940, is added. The book contains many excellent illustrations with several color plates.

IRVING PUNTENNEY.

THE second edition of a volume published 2 years ago under the title of *Gynecology and Female Endocrinology*, now appears as a *Textbook of Gynecology*[2]; actually it is more than that. It is an expansion into an admirable textbook for medical students and general practitioners. While only 2 new chapters have been added, they represent a real advance. One is a chapter on embryology of the female generative tract which consolidates considerable material which was scattered throughout the original work. The second on common disorders of the female urinary organs is written by Dr. Houston S. Everett. It is well done, but could have been more inclusive, and it is hoped that a future edition will remedy this incompleteness.

Novak has redistributed the material in this text to good advantage. The space devoted to anatomy, history taking, and examination methods has been reduced, and the space gained has been excellently devoted to pathology, endocrinology, and the so called functional disorders. There is a profusion of illustrations, many of them in color, a factor which helps to make the text valuable. Special mention should be made of the chapters dealing with normal and abnormal menstruation, the menopause, sterility, and the problems of sex life. They are true reflections of the sanity and common sense which have always characterized therapy as recommended and practiced by the author.

All these assets when summed up make a complete picture. This textbook is most heartily recommended to those for whom the author has written it: viz., medical students and general practitioners.

RALPH A. REIS.

[1] INDUSTRIAL OPHTHALMOLOGY. By Hedwig S. Kuhn, M.D. St. Louis: The C. V. Mosby Co., 1944.

[2] TEXTBOOK OF GYNECOLOGY. By Emil Novak, M.D., F.A.C.S. 2d ed. Baltimore: The Williams & Wilkins Co., 1944.

AN excellent, up to date, small, compact textbook which contains the most recent knowledge pertaining to tuberculosis of the ear, nose, and throat, including the larynx, trachea, and bronchi has been written by Dr. Myerson.[1]

The various phases of tuberculosis are described and discussed completely as to diagnosis, prognosis, pathology, and treatment. To enhance the discussion, there are many tables of statistics, abundant case histories, and a goodly number of very excellent illustrations all of which are of great assistance. The author has gone to great length carefully to describe the many forms of therapeutic measures which have been advocated, those which have survived and those which have failed.

In discussing bronchoscopy in tuberculous patients the author from his vast experience has found that certain patients are very definitely improved by such a procedure while others suffer detrimental effects. To overcome this harmful result the author has developed a special technique described in detail.

The chapter discussing nontuberculous diseases of the ear, nose, and throat portrays the various types of lesions which may occur in a tuberculous patient. Thus the reader is cautioned to be on the look-out for such lesions even though the patient is a tuberculous one.

This book is most enlightening and refreshing.

LINN F. MCBRIDE.

[1] TUBERCULOSIS OF THE EAR, NOSE, AND THROAT; INCLUDING THE LARYNX, THE TRACHEA, AND THE BRONCHI. By Mervin C. Myerson, M.D. Springfield, Ill., and Baltimore, Md.: Charles C. Thomas, 1944.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

SURGERY OF THE HAND. By Sterling Bunnell, M.D. Philadelphia, London, Montreal: J. B. Lippincott Company, 1944.

GYNECOLOGICAL AND OBSTETRICAL UROLOGY. By Houston E. Everett, A.B., A.M., M.D. Baltimore: The Williams & Wilkins Company, 1944.

PRINCIPLES AND PRACTICE OF SURGERY. By W. Wayne Babcock, M.D. Philadelphia, Lea & Febiger, 1944.

THE SOUTH AFRICAN FROG (XENOPUS LAEVIS) IN PREGNANCY DIAGNOSIS. By Abner I. Weisman, M.D. and Christopher W. Coates. New York: Clark & Fritts, 1944.

DICTIONARY OF GYNECOLOGY AND OBSTETRICS. By Clarence Wilbur Taber, with the colloboration of Mario A. Castallo, M.D., F.A.C.S. Philadelphia: F. A. Davis Company, Publishers, 1944.

THE 1944 YEAR BOOK OF RADIOLOGY. By Dr. Ira I. Kaplan, B.Sc., Dr. Charles A. Waters, Dr. Whitmer B. Firor. Chicago: The Year Book Publishers, 1944.

STRUCTURE AND FUNCTION AS SEEN IN THE FOOT. By Frederick Wood Jones, Sc.D., F.R.S., F.R.C.S. Baltimore: The Williams and Wilkins Co., 1944.

PLASTER OF PARIS TECHNIC. By Edward Geckeler, M.D. Baltimore: The Williams & Wilkins Co., 1944.

TEMAS DE CIRUGIA DE URGENCIA. By P. Larghero Ybarz. Montevideo: Libreros Editores: A. Monteverde Y Cia, 1944.

THE URINARY TRACT, A HANDBOOK OF ROENTGEN DIAGNOSIS. By. H. Dabney Kerr, M.D., and Carl L. Gillies, M.D. Chicago: The Year Book Publishers, 1944.

GYNECOLOGY AND GYNECOLOGIC NURSING. By Norman F. Miller, M.D., Virginia Bryant, R.N., and Molly Kowal, R.N. Philadelphia and London: W. B. Saunders Co., 1944.

OPERATIONS OF GENERAL SURGERY. By Thomas G. Orr, M.D., Philadelphia and London: W. B. Saunders Company, 1944.

FUNDAMENTALS OF INTERNAL MEDICINE, 2d ed. By Wallace Mason Yater, A.B., M.D., M.S., F.A.C.P. New York, London: D. Appleton Century Company, 1944.

THE DISEASES OF THE ENDOCRINE GLANDS. By Herman Zodeck, M.D. (German), translated by Carl P. Giles, M.D., M.R.C.S., L.R.C.P. Baltimore: A William Wood Book, The Williams and Wilkins Company, 1944.

ORTHOPAEDIC SURGERY. By Walter Mercer, M.B., Ch.B., F.R.C.S., F.R.S. Baltimore: A William Wood Book, The Williams & Wilkins Book Company, 1943.

INTRACRANIAL ARTERIAL ANEURYSMS. By Walter E. Dandy. Ithaca, N. Y.: Comstock Publishing Co., Inc., 1944.

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[1]*Meyer, E., and Arnold, L., 1938, Amer. Digest. Dis., 5:412.*

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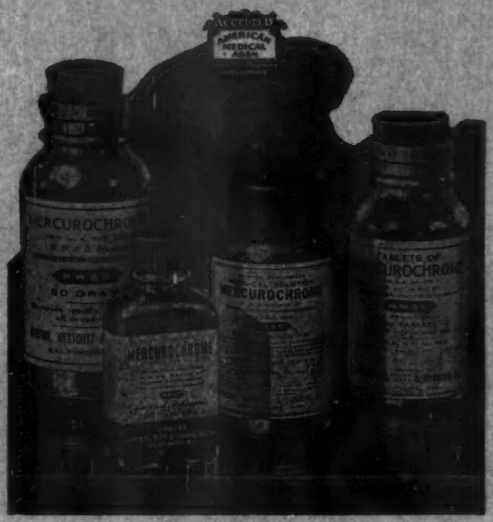

Mercurochrome
(H. W. & D. Brand of merbromin, dibrom-oxymercuri-fluorescein-sodium)

is economical because stock solutions may be dispensed quickly and at low cost by the physician or in the dispensary. Stock solutions keep indefinitely.

Mercurochrome is accepted by the Council on Pharmacy and Chemistry of the American Medical Association. Literature furnished to physicians on request.

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